STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 156447

TO: Jennifer Kim **Location: 4b02 / 4b18** **Tuesday, June 21, 2005** **Art Unit: 1617** **Phone: 571-272-0628** **Serial Number: 10 / 731375**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Remsen 1a51** **Phone: 571-272-2504** **jan.delaval@uspto.gov**

Search Notes

12/6/2002

Jen Kelwood

Access DB# 156449

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Jennifer Kim Examiner #: 77469 Date: 6/14/05
Art Unit: 1617 Phone Number 30[illegible]0628 Serial Number: 10/731,375
Mail Box and Bldg Room Location: Rem 4B02 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Methods and Composition for treatment of otitis media

Inventors (please provide full names): Barr et al.

Earliest Priority Filing Date: 12/6/2002

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search claims 13 – 17, + 8, 11, ~~20~~.

THX,

jr

BEST AVAILABLE COPY

STAFF USE ONLY

Searcher: [illegible]
Searcher Phone #: 22504
Searcher Location:
Date searcher picked up: 6/21/06
Date completed: 6/21/06
Searcher Prep & Review Time:
Clerical Prep Time: 20
Online Time: +120

Type of Search

NA Sequence (#)
AA Sequence (#)
Structure (#)
Bibliographic: ✓
Litigation
Fulltext
Patent Family
Other

Vendors and cost where applicable

STN: ✓
Dialog
Questel/Orbit:
Dr. Link:
Lexis/Nexis:
Sequence Systems:
WWW/Internet:
Other (specify):

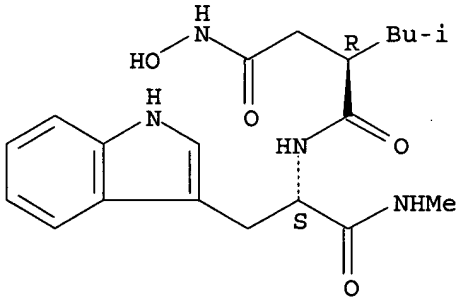
```
=> d his

     (FILE 'HOME' ENTERED AT 14:02:58 ON 21 JUN 2005)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 14:03:04 ON 21 JUN 2005
L1             1 S US20040175383/PN OR (US2003-731375# OR WO2003-US39053 OR US20
               E BARR P/AU
L2           259 S E3,E7,E22-30
               E PEMBERTON P/AU
L3            34 S E3,E4,E8,E10
               E ANTONELLI P/AU
L4            12 S E3,E7
               E SCHULTZ G/AU
L5           208 S E3,E13
               E SCHULTZ GREG/AU
L6            94 S E3-E5,E8,E9
               E SUNDIN D/AU
L7            10 S E7,E8
               E ARRIVA/PA,CS
L8             9 S E3-E10
               E U FL/PA,CS
               E U OF FL/PA,CS
               E UN FL/PA,CS
               E UN OF FL/PA,CS
               E UNI FL/PA,CS
               E UNI OF FL/PA,CS
               E UNIV FL/PA,CS
L9            15 S E5-E10
               E UNIV OF FL/PA,CS
L10           59 S E5-E8,E10-E24
L11         4780 S E25-E79
               E UNIVER FL/PA,CS
               E UNIVER OF FL/PA,CS
               E UNIVERS FL/PA,CS
               E UNIVERS OF FL/PA,CS
               E UNIVERSITY FL/PA,CS
L12           56 S E6-E18
               E UNIVERSITY OF FL/PA,CS
L13         1247 S E33-E205
               E FLORIDA/PA,CS
L14        69197 S E3,E4

     FILE 'REGISTRY' ENTERED AT 14:09:55 ON 21 JUN 2005
L15            1 S ILOMASTAT/CN
               E C20H28N4O4/MF
L16           32 S E3 AND NC4-C6/ES AND 2/NR
L17            7 S L16 AND BUTANEDIAMIDE
L18            6 S L17 NOT 200866-76-8
L19            6 S L15,L18
               SEL RN
L20            0 S E1-E6/CRN
L21          674 S (?MATRIX?(L)?METALLO?(L)(?PROTEINASE? OR ?PROTEASE?))/CNS
L22          583 S (?MATRIX?(L)(?METALLOPROTEINASE? OR ?METALLOPROTEASE?))/CNS
               E MMP
L23          790 S E3-E102
L24          674 S L21,L22
L25          349 S L24 AND L23
L26          674 S L24,L25
L27          441 S L23 NOT L26
```

```
                E ANTITRYPSIN
L28          83 S E3
L29          85 S ANTI TRYPSIN
                E AAT
L30         452 S E3
                E SCAN
                E RAAT
L31           4 S L30 AND L28,L29
L32         141 S ALPHA()1()(ANTITRYPSIN OR ANTI TRYPSIN OR TRYPSIN INHIBIT?)

     FILE 'HCAPLUS' ENTERED AT 14:18:38 ON 21 JUN 2005
L33       20912 S L28-L32
L34        5525 S ALPHA()1()(ANTITRYPSIN OR ANTI TRYPSIN)
L35        5582 S ALPHA()1(L)(ANTITRYPSIN OR ANTI TRYPSIN)
L36        1441 S ALPHA()1(L)TRYPSIN(L)INHIBIT?
L37       22445 S L33-L36
L38       43494 S L26 OR L27
L39       15830 S ?MATRIX?(L)?METALLO?(L)(?PROTEINASE? OR ?PROTEASE?)
L40       15738 S ?MATRIX?(L)(?METALLOPROTEINASE? OR ?METALLOPROTEASE?)
L41          15 S ?MATRIXMETALLO?(L)(?PROTEINASE? OR ?PROTEASE?)
L42          15 S ?MATRIXMETALLOPROTEINASE? OR ?MATRIXMETALLOPROTEASE?
L43       13586 S MMP?
L44       48294 S L38-L43
L45         100 S L19
L46         215 S ILOMASTAT OR CS610 OR CS 610 OR GM6001 OR GM 6001 OR GALARDIN
L47         227 S L45,L46
                E OTITIS/CT
                E E3+ALL
L48         471 S E1,E2,E3
                E OTITI? MEDI?
L49        1294 S OTITI? MEDI?
L50        1656 S E12
                E TYMPANIC MEMBRANE/CT
                E E3+ALL
L51         112 S E2
L52         407 S TYMPAN?(L)MEMBRAN?
                E AUDITORY CANAL/CT
L53         116 S AUDITORY CANAL
                E MIDDLE EAR
                E MIDDLE EAR/CT
                E E3+ALL
L54         439 S E2
                E TYMPANOSOMY/CT
                E TYMPANOSTOMY/CT
L55          35 S TYMPANOSTOM?
                E OTORRHEA/CT
                E OTORRHEA
L56          37 S E3-E5
                E EAR/CT
L57        9213 S E3-E63
L58       12277 S E3+OLD,NT,PFT,RT OR E54+OLD,NT,PFT,RT
L59       12960 S L48-L58
L60          23 S L59 AND L37
L61          73 S L59 AND L44
L62           2 S L59 AND L47
L63           4 S L1-L14 AND L60-L62
                E PEMBERTON P/AU
L64          37 S E3,E4,E9,E10
L65           4 S L64 AND L60-L62
L66           4 S L63,L65
```

```
L67          84 S L60-L62 NOT L66
L68          76 S L67 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L69          19 S L68 AND L37
L70           5 S L69 AND L44
L71           0 S L69 AND L47
L72          19 S L69,L70
               SEL DN AN 3-5 10-12 15 16
L73           8 S L72 AND E1-E24
L74          57 S L68 NOT L69-L73
               SEL DN AN 17 37 48 49 L74
L75           4 S E25-E36 AND L74
L76           3 S L75 NOT 3/SC
L77          15 S L66,L73,L76 AND L1-L14,L33-L76
               SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 14:52:28 ON 21 JUN 2005
L78           6 S E37-E42
L79           1 S L78 AND L19
L80           4 S L78 AND L26,L27
L81           1 S L78 AND L28-L32

=> fil reg
FILE 'REGISTRY' ENTERED AT 14:53:40 ON 21 JUN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   20 JUN 2005  HIGHEST RN 852602-49-4
DICTIONARY FILE UPDATES:  20 JUN 2005  HIGHEST RN 852602-49-4

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*********************************************************************
*                                                                   *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
*********************************************************************

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d l79 ide can

L79  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   142880-36-2  REGISTRY
```

ED Entered STN: 12 Aug 1992
CN **Butanediamide, N4-hydroxy-N1-[(1S)-1-(1H-indol-3-ylmethyl)-2-(methylamino)-2-oxoethyl]-2-(2-methylpropyl)-, (2R)- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Butanediamide, N4-hydroxy-N1-[1-(1H-indol-3-ylmethyl)-2-(methylamino)-2-oxoethyl]-2-(2-methylpropyl)-, [S-(R*,S*)]-**
OTHER NAMES:
CN CS 610
CN Galardin
CN GM 6001
CN **Ilomastat**
FS STEREOSEARCH
MF **C20 H28 N4 O4**
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, MEDLINE, PHAR, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
Other Sources: WHO

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

99 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
100 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:456684

REFERENCE 2: 142:211519

REFERENCE 3: 142:162531

REFERENCE 4: 142:127629

REFERENCE 5: 142:127066

REFERENCE 6: 142:48885

REFERENCE 7: 142:48821

REFERENCE 8: 142:32962

REFERENCE 9: 142:723

REFERENCE 10: 141:376783

=> d l80 ide can tot

L80 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN **146480-36-6** REGISTRY
ED Entered STN: 17 Mar 1993
CN Gelatinase B (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 92,000-Mol.-wt. gelatinase
CN 92,000-Mol.-wt. type IV collagenase
CN 92-kD Gelatinase
CN 92-kDa Gelatinase
CN 92-kDa Type IV collagenase
CN 95 kDa Type IV collagenase/gelatinase
CN Collagenase IV
CN Collagenase type IV
CN E.C. 3.4.24.35
CN **Gelatinase MMP 9**
CN **Matrix metalloprotease 9**
CN **Matrix metalloproteinase-9**
CN **MMP 9**
CN Type IV collagen metalloproteinase
CN Type IV collagenase
CN Type IV collagenase/gelatinase
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN, CHEMCATS, CIN, EMBASE, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
5379 REFERENCES IN FILE CA (1907 TO DATE)
14 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5407 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:487357

REFERENCE 2: 142:480688

REFERENCE 3: 142:480618

REFERENCE 4: 142:480447

REFERENCE 5: 142:480417

REFERENCE 6: 142:479893

REFERENCE 7: 142:479796

REFERENCE 8: 142:479666

REFERENCE 9: 142:479600

REFERENCE 10: 142:479554

L80 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN **146480-35-5** REGISTRY
ED Entered STN: 17 Mar 1993
CN Gelatinase A (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 72 kDa Gelatinase
CN 72 kDa Gelatinase type A
CN 72,000-Mol.-wt. gelatinase
CN 72,000-Mol.-wt. type IV collagenase
CN Collagenase IV
CN Collagenase type IV
CN E.C. 3.4.24.24
CN **Matrix metalloprotease 2**
CN **Matrix metalloproteinase 2**
CN **MMP 2**
CN Type IV collagen metalloproteinase
CN Type IV collagenase
CN Type IV collagenase/gelatinase
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN, CHEMCATS, CIN, EMBASE, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5425 REFERENCES IN FILE CA (1907 TO DATE)
14 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5444 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:487357

REFERENCE 2: 142:480688

REFERENCE 3: 142:480417

REFERENCE 4: 142:479901

REFERENCE 5: 142:479835

REFERENCE 6: 142:479796

REFERENCE 7: 142:479759

REFERENCE 8: 142:479697

REFERENCE 9: 142:479666

REFERENCE 10: 142:479600

L80 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN **9004-06-2** REGISTRY
ED Entered STN: 16 Nov 1984
CN Elastase (9CI) (CA INDEX NAME)
OTHER NAMES:
CN E.C. 3.4.21.11

CN E.C. 3.4.21.36
CN E.C. 3.4.21.37
CN E.C. 3.4.24.65
CN E.C. 3.4.4.7
CN Elaszym
CN Macrophage metalloelastase
CN **Matrix metalloprotease 12**
CN **Matrix metalloproteinase-12**
CN Medullasin
CN Metalloproteinase HME
CN **MMP 12**
CN Neutrophil Elastase
CN Pancreatopeptidase E
CN Peptidase, pancreato-, E
CN Proteinase, bone marrow serine
DR 9001-21-2, 139074-64-9, 75603-19-9, 83682-98-8
MF Unspecified
CI COM, MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, NAPRALERT, NIOSHTIC, PHAR, PIRA, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8817 REFERENCES IN FILE CA (1907 TO DATE)
286 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
8831 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:487681

REFERENCE 2: 142:480766

REFERENCE 3: 142:480732

REFERENCE 4: 142:477174

REFERENCE 5: 142:476193

REFERENCE 6: 142:476177

REFERENCE 7: 142:475648

REFERENCE 8: 142:461611

REFERENCE 9: 142:461532

REFERENCE 10: 142:461258

L80 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN **9001-12-1** REGISTRY
ED Entered STN: 16 Nov 1984
CN Collagenase (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Aspergillopeptidase C

CN Azocollase
CN Clostridiopeptidase A
CN Clostridiopeptidase I
CN Clostridiopeptidase II
CN Clostridium histolyticum collagenase
CN Collagen peptidase
CN Collagen protease
CN Collagenase A
CN **Collagenase MMP-1**
CN E.C. 3.4.24.3
CN E.C. 3.4.24.34
CN E.C. 3.4.24.7
CN E.C. 3.4.4.19
CN E.C. 3.4.99.5
CN Euphaulysin
CN FPM-MP
CN Interstitial collagenase
CN Iruxol
CN Kollaza
CN Liberase
CN Liberase Blendzyme IV
CN Liberase PI
CN **Matrix metalloprotease MMP-ABT**
CN **Matrix metalloprotease-1**
CN **Matrix metalloproteinase-1**
CN **Matrix metalloproteinase-18**
CN **Matrix metalloproteinase-8**
CN Metallocollagenase
CN Metalloproteinase-1
CN **MMP-1**
CN **MMP-8**
CN Morikraz
CN Nucleolysin
CN Peptidase, clostridio-, A
CN Proteinase, Clostridium histolyticum, A
CN Santyl
CN Soycollagestin
DR 37288-86-1, 39433-96-0
MF Unspecified
CI COM, MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PIRA, PROMT, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9076 REFERENCES IN FILE CA (1907 TO DATE)
79 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
9090 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:487693

REFERENCE 2: 142:487681

REFERENCE 3: 142:487569

REFERENCE 4: 142:487205

REFERENCE 5: 142:480766

REFERENCE 6: 142:479692

REFERENCE 7: 142:479593

REFERENCE 8: 142:479317

REFERENCE 9: 142:478226

REFERENCE 10: 142:477174

=> d l81 ide can

L81 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN **9041-92-3** REGISTRY
ED Entered STN: 16 Nov 1984
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN α-1-Protease inhibitor
CN α1-Antiprotease
CN α1-Antiproteinase
CN **α1-Antitrypsin**
CN **α1-Antitrypsin Pittsburgh mutant**
CN **α1-Antitrypsin Portland**
CN α1-AT
CN α1-Protease inhibitor
CN α1-Proteinase inhibitor
CN **α1-Trypsin inhibitor**
CN **Antitrypsin Pittsburgh**
CN Prolastin
CN Respitin
CN SERPINA1
DR 9082-50-2, 124542-00-3
MF Unspecified
CI COM, MAN
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSRESEARCH, IPA, MRCK*, NIOSHTIC, PHAR, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5527 REFERENCES IN FILE CA (1907 TO DATE)
311 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5538 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:487503

REFERENCE 2: 142:487376

REFERENCE 3: 142:487367

REFERENCE 4: 142:480981

REFERENCE 5: 142:476291

REFERENCE 6: 142:476252

REFERENCE 7: 142:476066

REFERENCE 8: 142:469309

REFERENCE 9: 142:462323

REFERENCE 10: 142:461387

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 14:54:03 ON 21 JUN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 21 Jun 2005 VOL 142 ISS 26
FILE LAST UPDATED: 20 Jun 2005 (20050620/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all hitstr tot l77

L77 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:739746 HCAPLUS
DN 141:230746
ED Entered STN: 10 Sep 2004
TI Methods and compositions for treatment of **otitis media**
IN **Barr, Philip J.; Pemberton, Philip A.; Antonelli, Patrick J.; Schultz, Gregory S.; Sundin, David J.**
PA USA
SO U.S. Pat. Appl. Publ., 12 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K039-395
ICS A61K031-56

INCL 424146100; 514171000; 424046000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004175383	A1	20040909	US 2003-731375	20031208 <--
	WO 2004052236	A2	20040624	WO 2003-US39053	20031208 <--
	WO 2004052236	A3	20040826		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI	US 2002-431286P	P	20021206	<--
	US 2002-435985P	P	20021220	<--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004175383	ICM	A61K039-395
	ICS	A61K031-56
	INCL	424146100; 514171000; 424046000
US 2004175383	NCL	424/146.100; 514/171.000; 424/046.000 <--

AB The invention is directed to the treatment of **otitis media** by administration of **protease** inhibitors. In some embodiments, the **protease** inhibitors are alpha one-**antitrypsin** and/or **ilomastat**.. The effects of . **alpha.1-antitrypsin** and **ilomastat** on **matrix metalloproteinases** and human neutrophil elastase activities in middle ear effusion samples were collected from patients with **otitis media** were examined Also, a solution composition containing recombinant **.alpha.1-antitrypsin** 51.65 mg/mL, KCl 200 mEq/L, sodium phosphate 0.02, sodium citrate 0.005, and N-acetyl cysteine 0.005 M was formulated.

ST protease inhibitor **otitis media** treatment; antitrypsin **otitis media** treatment

IT Neoplasm
(cholesteatoma; methods and compns. for treatment of **otitis media** with protease inhibitors)

IT Antibiotics
Human
(methods and compns. for treatment of **otitis media** with protease inhibitors)

IT Steroids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. for treatment of **otitis media** with protease inhibitors)

IT **Ear, disease**
(**neoplasm, cholesteatoma**; methods and compns. for treatment of **otitis media** with protease inhibitors)

IT **Ear, disease**
Inflammation
(**otitis media**; methods and compns. for treatment of **otitis media** with protease inhibitors)

IT **Ear, disease**

Inflammation
(**otitis**; methods and compns. for treatment of **otitis media** with protease inhibitors)
IT Drug delivery systems
(powders, dry; methods and compns. for treatment of **otitis media** with protease inhibitors)
IT Drug delivery systems
(solns., ear; methods and compns. for treatment of **otitis media** with protease inhibitors)
IT **9004-06-2**, Neutrophil elastase **146480-35-5**, **Matrix metalloproteinase** 2 **146480-36-6**, **Matrix metalloproteinase** 9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(methods and compns. for treatment of **otitis media** with **protease** inhibitors)
IT **9041-92-3 142880-36-2, Ilomastat**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. for treatment of **otitis media** with protease inhibitors)
IT **9004-06-2**, Neutrophil elastase **146480-35-5**, **Matrix metalloproteinase** 2 **146480-36-6**, **Matrix metalloproteinase** 9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(methods and compns. for treatment of **otitis media** with **protease** inhibitors)
RN 9004-06-2 HCAPLUS
CN Elastase (9CI) (CA INDEX NAME)

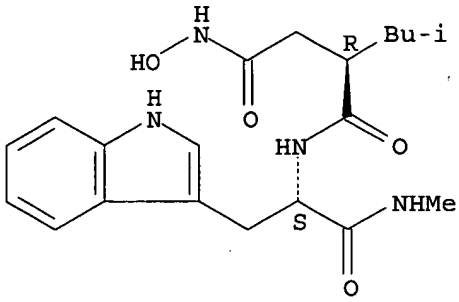
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-35-5 HCAPLUS
CN Gelatinase A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-36-6 HCAPLUS
CN Gelatinase B (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9041-92-3 142880-36-2, Ilomastat**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. for treatment of **otitis media** with protease inhibitors)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 142880-36-2 HCAPLUS
CN Butanediamide, N4-hydroxy-N1-[(1S)-1-(1H-indol-3-ylmethyl)-2-(methylamino)-2-oxoethyl]-2-(2-methylpropyl)-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L77 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:453045 HCAPLUS
DN 141:12313
ED Entered STN: 04 Jun 2004
TI Compositions containing protease inhibitors for treating inflammatory diseases
IN Bathurst, Ian C.; **Pemberton, Philip A.**; **Sundin, David J.** ; Mayhew, James W.; Angel, Arturo J.; **Barr, Philip J.**
PA **Arriva**-Prometic Inc., Can.
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004045634	A1	20040603	WO 2003-GB5049	20031120

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2002-427702P P 20021120

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004045634	ICM	A61K038-00
WO 2004045634	ECLA	A61K038/55; A61K038/57

AB Compns. containing a protease inhibitor and methods of use and production are described. The compns. contain an effective amount of a protease inhibitor in a carrier or diluent and are used for the treatment of inflammatory or hyperproliferative skin disorders. The carrier or diluent is preferably a gelling agent, and the composition is a topical gel formulation containing . **alpha.-1-antitrypsin** in an aqueous liquid or viscous gel formulation. Thus, a formulation contained **antitrypsin** 10.0, benzyl alc. 1.0, hydroxyethyl cellulose 2.0, and water 97.0%.

ST protease inhibitor inflammatory disease; **alpha 1**

antitrypsin inflammatory disease topical gel

IT Carcinoma
Skin, neoplasm
(Bowen's disease; compns. containing protease inhibitors for treating inflammatory diseases)

IT Sarcoma
(Kaposi's; compns. containing protease inhibitors for treating inflammatory diseases)

IT Skin, disease
(aging; compns. containing protease inhibitors for treating inflammatory diseases)

IT Dermatitis
(atopic; compns. containing protease inhibitors for treating inflammatory diseases)

IT Skin, neoplasm
(basal cell carcinoma; compns. containing protease inhibitors for treating inflammatory diseases)

IT Carcinoma
(basal cell; compns. containing protease inhibitors for treating inflammatory diseases)

IT Inflammation
Intestine, disease
(colitis; compns. containing protease inhibitors for treating inflammatory diseases)

IT Acne
Dermatitis
Digestive tract, disease
Ear, disease
Eye, disease
Gelation agents
Inflammation
Keratosis
Psoriasis
Stability
Ulcer
Urinary tract, disease
(compns. containing protease inhibitors for treating inflammatory **diseases**)

IT Peptides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. containing protease inhibitors for treating inflammatory diseases)

IT Eye, disease
Inflammation
(conjunctivitis; compns. containing protease inhibitors for treating inflammatory diseases)

IT Drug delivery systems
(gels, topical; compns. containing protease inhibitors for treating inflammatory diseases)

IT Skin, disease
(hyperproliferation; compns. containing protease inhibitors for treating inflammatory diseases)

IT Skin, disease
(irritation; compns. containing protease inhibitors for treating inflammatory diseases)

IT Skin, disease
(lichen planus; compns. containing protease inhibitors for treating inflammatory diseases)

IT **Ear, disease**
Inflammation
(**otitis**; compns. containing protease inhibitors for treating

inflammatory **diseases**)
IT Carcinoma
(squamous cell; compns. containing protease inhibitors for treating inflammatory diseases)
IT Burn
(wound; compns. containing protease inhibitors for treating inflammatory diseases)
IT **9041-92-3**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. containing protease inhibitors for treating inflammatory diseases)
IT 9003-01-4, Poly(acrylic acid) 9004-62-0, Hydroxyethyl cellulose
9004-64-2, Hydroxypropyl cellulose 106392-12-5, Pluronic
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gelling agent; compns. containing protease inhibitors for treating inflammatory diseases)
IT 9001-92-7, Protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; compns. containing protease inhibitors for treating inflammatory diseases)
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Biotech Australia Pty Ltd; WO 9949887 A 1999 HCAPLUS
(2) Ceskoslovenska Akademie Ved; EP 0420600 A 1991 HCAPLUS
(3) Johnson & Johnson Medical; GB 2318732 A 1998 HCAPLUS
(4) Lezdey, J; WO 9206706 A 1992 HCAPLUS
(5) Nanosystems Llc; WO 9902665 A 1999 HCAPLUS
(6) Quay, S; WO 0130380 A 2001 HCAPLUS
(7) Sharp, P; WO 0007620 A 2000 HCAPLUS
(8) Us Agriculture; WO 0164132 A 2001
(9) Yamazaki, T; JP 57145817 A 1982 HCAPLUS
IT **9041-92-3**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. containing protease inhibitors for treating inflammatory diseases)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:592821 HCAPLUS
DN 140:104733
ED Entered STN: 04 Aug 2003
TI **Alpha 1-Antitrypsin** and **Ilomastat**
Inhibit Inflammatory Proteases Present in Human Middle Ear Effusions
AU **Antonelli, Patrick J.**; **Schultz, Gregory S.**; Kim, Karen M.; Cantwell, John S.; **Sundin, David J.**; **Pemberton, Philip A.**; **Barr, Philip J.**
CS Department of Otolaryngology, University of **Florida**, Gainesville, FL 32610, USA
SO Laryngoscope (2003), 113(8), 1347-1351
CODEN: LARYA8; ISSN: 0023-852X
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 1-7 (Pharmacology)
Section cross-reference(s): 14
AB **Proteases** of both the serine and **metalloproteinase** families have been shown to play a role in the pathogenesis of **otitis media** (OM). Inhibitors of **proteases** from each of these families have been shown to beneficially impact disease

progression in a number of related chronic inflammatory conditions, but their use has not been studied in OM. The purpose of this study was to assess the activity of the **protease** inhibitors recombinant **alpha 1-antitrypsin** (rAAT) and **ilomastat** on inflammatory **proteases** present in human middle ear effusions (MEEs), with a view to their potential utility in the treatment of OM. The study design was prospective and ex vivo. MEEs were collected from 100 patients presenting for middle ear surgery, most commonly **tympanostomy** tube placement or treatment of acute post-**tympanostomy otorrhea** (APTO). MEEs were analyzed for the presence of **matrix metalloproteinases** (**MMPs**) and human neutrophil elastase (HNE) and the inhibitory activity of rAAT and **ilomastat** on these **proteases**, resp. **MMP** levels were highest in APTO, and HNE was highest in chronic suppurative OM and APTO. High levels of **MMP** and HNE (>3 mAU/min) were found in 52% and 37% of MEEs, resp. **Ilomastat** and rAAT demonstrated significant inhibition of **MMP** and HNE activity (>30% reduction), resp., in 80% and 82% of MEEs with high levels of activity. **Proteases** are commonly found in OM. **Ilomastat** and rAAT are potent inhibitors of **proteases** in MEEs across a wide range of OM in humans. Investigation into the potential therapeutic benefits of these **protease** inhibitors is warranted.

ST antitrypsin alpha1 **ilomastat** inhibitor inflammatory proteinase middle ear effusion; **otitis media** effusion inflammatory proteinase inhibitor alpha1 antitrypsin **ilomastat**

IT **Ear, disease**
Inflammation
(**otitis media**; α **1-antitrypsin** and **ilomastat** inhibit inflammatory proteinases present in human **middle** ear effusions)

IT Human
(α **1-antitrypsin** and **ilomastat** inhibit inflammatory proteinases present in human middle ear effusions)

IT **9004-06-2**, Neutrophil elastase **146480-35-5**, **Matrix metalloproteinase**-2 **146480-36-6**, **Matrix metalloproteinase**-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition; α **1-antitrypsin** and **ilomastat** inhibit inflammatory **proteinases** present in human middle ear effusions)

IT **9041-92-3**, α **1-Antitrypsin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(recombinant; α **1-antitrypsin** and **ilomastat** inhibit inflammatory proteinases present in human middle ear effusions)

IT **142880-36-2**, **Ilomastat**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α **1-antitrypsin** and **ilomastat** inhibit inflammatory proteinases present in human middle ear effusions)

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Alpagot, T; J Periodontal Res 2001, V36, P169 MEDLINE
(2) Antonelli, P; Laryngoscope (in press) 2003
(3) Avidano, M; Otolaryngol Head Neck Surg 1998, V119, P346 MEDLINE
(4) Brand, K; Curr Gene Ther 2002, V2, P255 HCAPLUS
(5) Carlsson, B; Acta Otolaryngol 1983, V95, P341 MEDLINE

(6) Cotter, C; Otolaryngol Head Neck Surg 1996, V115, P342 MEDLINE
(7) Doring, G; Pediatr Pulmonol 1999, V28, P363 MEDLINE
(8) Galardy, R; Ann N Y Acad Sci 1994, V732, P315 HCAPLUS
(9) Hamaguchi, Y; Ann Otol Rhinol Laryngol Suppl 1992, V157, P26 MEDLINE
(10) Heavner, S; Otolaryngol Head Neck Surg 2001, V125, P123 MEDLINE
(11) Hoyle, B; J Antimicrob Chemother 1990, V26, P1 HCAPLUS
(12) Hubbard, R; J Clin Invest 1989, V84, P1349 MEDLINE
(13) Jennings, C; Clin Otolaryngol 2001, V26, P491 MEDLINE
(14) Juhn, S; Ann Otol Rhinol Laryngol 1976, V85(2 Suppl 25 Pt 2), P110 MEDLINE
(15) Lehman, D; Otolaryngol Head Neck Surg 2002, V126, P273
(16) Lowell, S; Otolaryngol Head Neck Surg 1979, V87, P859 HCAPLUS
(17) Miyajima, S; Microb Pathog 2001, V31, P271 HCAPLUS
(18) Plaut, A; Vaccine 2000, V8(19(Suppl 1)), PS148
(19) Post, J; Laryngoscope 2001, V111, P2083 MEDLINE
(20) Scheiblauer, H; J Infect Dis 1992, V166, P783 MEDLINE
(21) Schmidt, M; Eur Arch Otorhinolaryngol 2001, V258, P472 MEDLINE
(22) Sebert, M; Infect Immun 2002, V70, P4059 HCAPLUS
(23) Stiskal, J; Pediatrics 1998, V101, P89 MEDLINE
(24) Tasker, A; Lancet 2002, V359, P493
(25) The Alpha-1-Antitrypsin Deficiency Registry Study Group; Am J Resp Crit Care Med 1998, V158, P49
(26) Tierney, P; Clin Otolaryngol 1995, V20, P230 MEDLINE
(27) Travis, J; J Biol Chem 1985, V260, P4384 HCAPLUS
(28) Trengove, N; Wound Repair Regen 1999, V7, P442 MEDLINE
(29) Wachter, A; Ann Allergy 1992, V69, P407 MEDLINE
(30) Weingarten, H; Anal Biochem 1985, V147, P437 HCAPLUS
(31) Wencker, M; Chest 2001, V119, P737 HCAPLUS
(32) Woods, D; Infect Immun 1982, V36, P1223 HCAPLUS

IT **9004-06-2**, Neutrophil elastase **146480-35-5**, **Matrix metalloproteinase**-2 **146480-36-6**, **Matrix metalloproteinase**-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition; α **1-antitrypsin** and **ilomastat** inhibit inflammatory **proteinases** present in human middle ear effusions)

RN 9004-06-2 HCAPLUS
CN Elastase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-35-5 HCAPLUS
CN Gelatinase A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-36-6 HCAPLUS
CN Gelatinase B (9CI) (CA INDEX NAME)

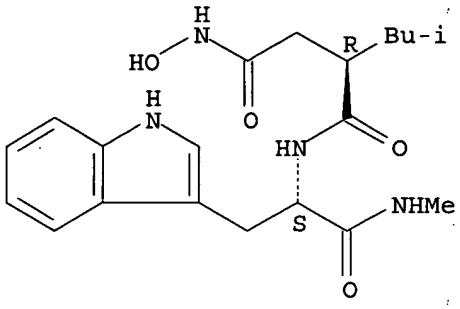
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9041-92-3**, α **1-Antitrypsin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(recombinant; α **1-antitrypsin** and **ilomastat** inhibit inflammatory proteinases present in human middle ear effusions)

RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **142880-36-2**, **Ilomastat**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(α **1-antitrypsin** and
ilomastat inhibit inflammatory proteinases present in human
middle ear effusions)
RN 142880-36-2 HCAPLUS
CN Butanediamide, N4-hydroxy-N1-[(1S)-1-(1H-indol-3-ylmethyl)-2-(methylamino)-2-oxoethyl]-2-(2-methylpropyl)-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L77 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2003:42066** HCAPLUS
DN **138:112442**
ED Entered STN: 17 Jan 2003
TI Compositions comprising bicarbonates and enzymes for removing human cerumen
IN Cagle, Gerald D.; Owen, Geoffrey R.; Ridruejo, Nuria Jimenez; Wall, G. Michael
PA Alcon, Inc., Switz.
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003003976	A2	20030116	WO 2002-US19756	20020621 <--
	WO 2003003976	A3	20030530		
	W: AU, BR, CA, CN, JP, KR, MX, NO, NZ, PH, PL, SG, US, ZA				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
	CA 2447886	AA	20030116	CA 2002-2447886	20020621 <--
	EP 1337228	A2	20030827	EP 2002-744528	20020621 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
	BR 2002010493	A	20040622	BR 2002-10493	20020621 <--
	US 2004126436	A1	20040701	US 2003-705441	20031110 <--
PRAI	US 2001-302959P	P	20010703 <--		
	WO 2002-US19756	W	20020621 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003003976	ICM	A61K
WO 2003003976	ECLA	A61K009/00M; A61K031/047+M; A61K033/00+M; A61K038/48; A61K038/48K1; A61K038/48K1+M; A61K038/48L+M; A61K045/06

<--

US 2004126436 NCL 424/717.000; 514/057.000
ECLA A61K009/00M; A61K031/047+M; A61K033/00+M; A61K038/48K1; A61K038/48K1+M; A61K038/48L; A61K038/48L+M; A61K045/06

<--

AB Compns. for assisting in the removal of human cerumen are disclosed. The compns. may include bicarbonate and an otol. acceptable vehicle; a cerumenolytically acceptable enzyme and an otol. acceptable vehicle; or bicarbonate, a cerumenolytically acceptable enzyme, and an otol. acceptable vehicle.

ST bicarbonate enzyme formulation human cerumen

IT Buffers
Human
Preservatives
Stabilizing agents
Surfactants
(compns. comprising bicarbonates and enzymes for removing human cerumen)

IT Enzymes, biological studies
Polyoxyalkylenes, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(compns. comprising bicarbonates and enzymes for removing human cerumen)

IT Fatty acids, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(esters; compns. comprising bicarbonates and enzymes for removing human cerumen)

IT **Ear**
(external; compns. comprising bicarbonates and enzymes for removing human cerumen)

IT Alkanes, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(long-chain, polyoxypropylene ethers; compns. comprising bicarbonates and enzymes for removing human cerumen)

IT Alcohols, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(polyhydric; compns. comprising bicarbonates and enzymes for removing human cerumen)

IT **Ear**
(**wax**; compns. comprising bicarbonates and enzymes for removing human cerumen)

IT 55-56-1D, Chlorhexidine, salts 56-81-5, Glycerin, biological studies 57-55-6, Propylene glycol, biological studies 71-52-3, Bicarbonate, biological studies 144-55-8, Sodium bicarbonate, biological studies 6132-04-3, Sodium citrate dihydrate 8049-47-6, Pancreatin 9000-92-4, Amylase **9001-12-1**, Collagenase 9001-62-1, Lipase 9001-73-4, Papain 9001-92-7, Protease 9002-07-7, Trypsin 9002-07-7D, Trypsin, alkyl derivs. 9002-07-7D, Trypsin, methylated derivs. 9002-89-5, Polyvinyl alcohol 9003-39-8, Povidone **9004-06-2**, Elastase 9004-34-6D, Cellulose, derivs. 9014-01-1, Subtilisin 9025-49-4 9031-94-1, Aminopeptidase 9031-98-5, Carboxypeptidase 9036-06-0, Pronase E 10043-35-3, Boric acid, biological studies 11129-12-7, Borate 14127-61-8, Calcium ion, biological studies 19010-47-0 22573-93-9D, Alexidine, salts 25322-68-3, Polyethylene glycol 37341-53-0, Keratinase 42613-33-2, Dispase 75345-27-6 106392-12-5, Polyoxyethylene-polyoxypropylene block copolymer 110617-70-4, Tetronic

1304 150977-36-9, Bromelain
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(compns. comprising bicarbonates and enzymes for removing human cerumen)
IT **9001-12-1**, Collagenase **9004-06-2**, Elastase
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(compns. comprising bicarbonates and enzymes for removing human cerumen)
RN 9001-12-1 HCAPLUS
CN Collagenase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9004-06-2 HCAPLUS
CN Elastase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:630455** HCAPLUS
DN **137:367821**
ED Entered STN: 22 Aug 2002
TI Genetic polymorphism of α1-inhibitor of proteinases in patients with chronic suppurative **otitis media** (COMS), and its complications
AU Shkorbotun, V. A.; Karpenko, G. F.; Goloborodko, O. P.
CS Kiev. Med. Akad., Kiev, Ukraine
SO Laboratorna Diagnostika (**2002**), (2), 22-26
CODEN: LDAIBX
PB Vidavnitstvo TOV "DIA"
DT Journal
LA Ukrainian
CC 14-10 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3
AB The paper presents some phenotypical variants and functional activity of α1-inhibitor of proteinases in blood serum of 148 patients with chronic **otitis media**, suppurative (COMS) and 110 healthy persons. The M2M2 phenotype occurs in patients with COMS 7 times as often as in the control group; the phenotypical variants - M1I, M1Z and ZZ - are determined in 3 patients with otogenic complications.
ST genetic polymorphism alpha1 inhibitor proteinase **otitis media**
IT Genetic polymorphism
Human
(genetic polymorphism of proteinase α1-inhibitor in human patients with suppurative chronic **otitis media** and its complications)
IT Blood serum
(genetic polymorphism of proteinase α1-inhibitor in human patients with suppurative chronic **otitis media** and its complications in relation to)
IT Allele frequency
Genotypes
Phenotypes
(of genetic polymorphism of proteinase α1-inhibitor in human patients with suppurative chronic **otitis media** and its complications)
IT **Ear, disease**
Inflammation

(**otitis media**, chronic suppurative; genetic polymorphism of proteinase α1-inhibitor in human patients with suppurative chronic **otitis media** and its complications)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(α1-proteinase inhibitor; genetic polymorphism of proteinase α1-inhibitor in human patients with suppurative chronic **otitis media** and its complications)

IT Macroglobulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α2-; genetic polymorphism of proteinase α1-inhibitor in human patients with suppurative chronic **otitis media** and its complications in relation to)

IT **9041-92-3**, Proteinase α1-inhibitor
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(genetic polymorphism of proteinase α1-inhibitor in human patients with suppurative chronic **otitis media** and its complications)

IT **9041-92-3**, Proteinase α1-inhibitor
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(genetic polymorphism of proteinase α1-inhibitor in human patients with suppurative chronic **otitis media** and its complications)

RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:487756 HCAPLUS
DN 137:57557
ED Entered STN: 28 Jun 2002
TI Fusion proteins of protease inhibitors and their use in treatment of inflammatory disease
IN **Barr, Philip J.**; Gibson, Helen L.; **Pemberton, Philip**
PA **Arriva Pharmaceuticals, Inc., USA**
SO PCT Int. Appl., 134 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-62
ICS C12N015-15; C07K014-81; A61K038-55; A61K038-57
CC 1-7 (Pharmacology)
Section cross-reference(s): 3, 7
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002050287	A2	20020627	WO 2001-US49256	20011218
	WO 2002050287	A3	20030918		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	CA 2430973	AA	20020627	CA 2001-2430973	20011218
	AU 2002041661	A5	20020701	AU 2002-41661	20011218
	US 2003073217	A1	20030417	US 2001-25514	20011218
	EP 1366175	A2	20031203	EP 2001-988344	20011218
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2004537970	T2	20041224	JP 2002-552164	20011218
PRAI	US 2000-256699P	P	20001218		
	US 2001-331966P	P	20011120		
	WO 2001-US49256	W	20011218		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002050287	ICM	C12N015-62
	ICS	C12N015-15; C07K014-81; A61K038-55; A61K038-57
WO 2002050287	ECLA	C07K014/81B1B1; C07K014/81B4; C07K014/81B1
US 2003073217	NCL	435/184.000; 435/069.700; 435/320.100; 435/325.000; 536/023.200
	ECLA	C07K014/81B1; C07K014/81B1B1; C07K014/81B4
JP 2004537970	FTERM	4B024/AA01; 4B024/AA11; 4B024/BA19; 4B024/CA04; 4B024/CA07; 4B024/DA02; 4B024/DA05; 4B024/DA06; 4B024/DA11; 4B024/DA12; 4B024/EA04; 4B024/GA11; 4B024/HA12; 4B064/AG23; 4B064/CA02; 4B064/CA05; 4B064/CA06; 4B064/CA10; 4B064/CA19; 4B064/CC24; 4B064/DA01; 4B065/AA01X; 4B065/AA57X; 4B065/AA72X; 4B065/AA90X; 4B065/AB01; 4B065/BA02; 4B065/CA24; 4B065/CA44; 4B065/CA46; 4C084/AA01; 4C084/AA02; 4C084/AA07; 4C084/BA02; 4C084/BA22; 4C084/DC32; 4C084/DC34; 4C084/DC50; 4C084/NA14; 4C084/ZA341; 4C084/ZA591; 4C084/ZA941; 4C084/ZC201; 4C084/ZC551; 4H045/AA10; 4H045/AA20; 4H045/AA30; 4H045/BA10; 4H045/BA41; 4H045/CA40; 4H045/DA56; 4H045/EA20; 4H045/EA29; 4H045/FA74

AB Fusion proteins of protease inhibitors are provided, in particular fusion proteins of **.alpha.1-antitrypsin** (AAT) and a second protease inhibitor, such as secretory leukocyte protease inhibitor (SLPI) or tissue inhibitor of metalloproteases (TIMP). Chimeric genes encoding the fusion proteins, and expression vectors and hosts for manufacture of the proteins are also provided. Methods of making the fusion proteins of the invention are also provide, as well as methods of using the fusion proteins, for example to inhibit protease activity in a biol. sample or in the treatment of an individual suffering from, or at risk for, a disease or disorder involving unwanted protease activity. The construction and expression of chimeric genes for a number of fusion proteins is described. Effective inhibition of elastase and tryptase by the fusion proteins is demonstrated.

ST proteinase inhibitor fusion protein inflammatory disease treatment; antitrypsin fusion protein inflammatory disease treatment; secretory leukocyte protease inhibitor fusion protein inflammatory disease treatment; TIMP1 antitrypsin fusion protein inflammatory disease treatment

IT Lung, disease
(chronic obstructive, protease inhibition in treatment of; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)

IT Saccharomyces cerevisiae
(expression host; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)

IT Chimeric gene, animal
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(for proteinase inhibitor fusion proteins; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT Human
(fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT Protein sequences
(of proteinase inhibitor fusion proteins of human; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT **Ear, disease**
Inflammation
(**otitis media**, protease inhibition in treatment of; fusion proteins of protease inhibitors and their use in treatment of inflammatory **disease**)
IT **Ear, disease**
Inflammation
(**otitis**, **otitis** externa, protease inhibition in treatment of; fusion proteins of protease inhibitors and their use in treatment of inflammatory **disease**)
IT AIDS (disease)
Asthma
Cystic fibrosis
Emphysema
Inflammation
(protease inhibition in treatment of; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT Anti-AIDS agents
(protease inhibitor fusion proteins as; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT Fermentation
(protein, of proteinase inhibitor fusion proteins, with yeast; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT 439122-04-0
RL: PRP (Properties)
(Unclaimed; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT 138729-66-5P 439122-02-8P 439540-54-2P 439540-55-3P 439540-56-4P 439540-57-5P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT **9041-92-3DP**, α **1-Antitrypsin**,
fusion proteins 122320-05-2DP, Secretory leukocyte protease inhibitor,
fusion proteins 140208-24-8DP, TIMP-1, fusion proteins
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT **9004-06-2**, Elastase 37259-58-8, Serine proteinase 37353-41-6, Cysteine proteinase 78169-47-8, Aspartyl proteinase 81669-70-7, Metalloproteinase 97501-93-4, Tryptase **146480-36-6**, **Matrix metalloproteinase** 9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic inhibition of; fusion proteins of **protease**

inhibitors and their use in treatment of inflammatory disease)
IT 439542-29-7, 1: PN: WO0250287 SEQID: 1 unclaimed DNA 439542-31-1, 3: PN: WO0250287 SEQID: 3 unclaimed DNA 439542-33-3, 5: PN: WO0250287 SEQID: 5 unclaimed DNA 439542-35-5, 7: PN: WO0250287 SEQID: 7 unclaimed DNA 439542-36-6, 8: PN: WO0250287 SEQID: 9 unclaimed DNA 439542-37-7, 9: PN: WO0250287 SEQID: 11 unclaimed DNA 439542-38-8 439542-39-9
439542-40-2 439542-41-3 439542-42-4 439542-44-6 439542-46-8
439542-48-0 439542-50-4 439542-54-8 439542-56-0
RL: PRP (Properties)
(unclaimed nucleotide sequence; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT 439542-30-0 439542-32-2 439542-34-4 439542-43-5 439542-45-7
439542-47-9 439542-49-1 439542-51-5 439542-53-7 439542-55-9
439542-57-1
RL: PRP (Properties)
(unclaimed protein sequence; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT 439542-52-6
RL: PRP (Properties)
(unclaimed sequence; fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
IT **9041-92-3DP**, α **1-Antitrypsin**,
fusion proteins
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(fusion proteins of protease inhibitors and their use in treatment of inflammatory disease)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9004-06-2**, Elastase **146480-36-6**, **Matrix metalloproteinase** 9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic inhibition of; fusion proteins of **protease** inhibitors and their use in treatment of inflammatory disease)
RN 9004-06-2 HCAPLUS
CN Elastase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-36-6 HCAPLUS
CN Gelatinase B (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2000:628010** HCAPLUS
DN **133:217681**
ED Entered STN: 10 Sep 2000
TI Inhibitors of serine protease activity, and methods and compositions for treatment of herpes virus infections
IN Shapiro, Leland
PA The Trustees of University Technology Corporation, USA
SO PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-08
ICS A61K038-57; A61P031-22

CC 1-5 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000051625	A1	20000908	WO 2000-US5557	20000303 <--

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI	US 1999-123167P	P	19990305 <--
	US 1999-153942P	P	19990915 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000051625	ICM	A61K038-08
	ICS	A61K038-57; A61P031-22
WO 2000051625	ECLA	A61K038/08; A61K038/57 <--

OS MARPAT 133:217681

AB Compns. and methods of treating and preventing a viral infection are provided. A method of blocking a viral infection facilitated by a serine proteolytic (SP) activity is disclosed, which involves administering to a subject suffering or about to suffer from a viral infection a therapeutically effective amount of a substance having serine protease inhibitory activity or serpin activity. Among the substances found to be useful are **.alpha.1-antitrypsin** (AAT), peptide derivs. from the carboxy terminal end of AAT and synthetic drugs mimicking the action of such substances. The invention is particularly well suited for checking a viral infection mediated by members of herpesviridae family.

ST antiviral herpes serine protease inhibitor; antitrypsin alpha1 antiviral herpes; peptide antitrypsin alpha1 antiviral herpes

IT AIDS (disease)
(AIDS-related lymphoma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Antitumor agents
(B-cell lymphoma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Antitumor agents
(Burkitt's lymphoma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Lymph node
(Castleman's disease; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Disease, animal
(Gardner's syndrome; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Nervous system
(Guillain-Barre syndrome; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Antitumor agents
Antitumor agents
(Hodgkin's disease inhibitors; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Antitumor agents

(Kaposi's sarcoma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Neoplasm
(Li-Fraumeni syndrome; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Antitumor agents
(T-cell lymphoma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Sulfones
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amidino; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Hyperplasia
(angiolymphoid; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Mouth
Mouth
(aphthous ulcer, inhibitors; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Antiulcer agents
(aphthous ulcer; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Dermatitis
(atopic; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Skin, neoplasm
(basal cell nevus syndrome; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Antitumor agents
(carcinoma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Uterus, neoplasm
Uterus, neoplasm
(cervix, inhibitors; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Antitumor agents
(cervix; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Disease, animal
(chills; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Cosmetics
(creams, and ointments; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Carboxylic acids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dicarboxylic, esters, phenylene dialkanoate esters; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Mouth
(disease, idiopathic burning mouth; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Mucous membrane
(disease; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Drugs

(gastrointestinal; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Gingiva
(gingivitis; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Mouth
(hairy leukoplakia; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Blood vessel, neoplasm
Blood vessel, neoplasm
(hemangiosarcoma, inhibitors; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Antitumor agents
(hemangiosarcoma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Nucleic acids
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(herpes viral; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Disease, animal
(herpes virus infection-caused; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Digestive tract
Eye, disease
Lung, disease
Mouth
Respiratory tract
Urogenital tract
(infection; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Hodgkin's disease
Hodgkin's disease
(inhibitors; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Eye, disease
(keratoconjunctivitis; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Transplant and Transplantation
Transplant and Transplantation
(kidney, epithelial tumors associated with; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Cosmetics
(lotions, and solns.; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Drug delivery systems
(lotions; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Lymph node
(lymphadenopathy, angioimmunoblastic; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Antitumor agents
(lymphoma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Disease, animal
(malaise; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Mesothelium
Mesothelium
(mesothelioma, inhibitors; serine protease inhibitors and methods and

compns. for treatment of herpes virus infections)
IT Antitumor agents
(mesothelioma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT **Ear**
(**middle**, infection; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Erythema
(multiforme; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Antitumor agents
(multiple myeloma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Antitumor agents
(nasopharynx carcinoma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Pharynx
Pharynx
(nasopharynx, carcinoma, inhibitors; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Prostate gland
Prostate gland
(neoplasm, inhibitors; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Nervous system
(neurofibromatosis type 1; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Nerve, disease
(neuropathy; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Drug delivery systems
(ointments, creams; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Drug delivery systems
(ointments; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Pharynx
(pharyngitis; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Neoplasm
(plexopathy from tumor infiltration; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Nerve, disease
(polyneuropathy; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Transplant and Transplantation
(post-transplantation lymphoproliferative disease; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Antitumor agents
(prostate gland; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Drug delivery systems
(rectal; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Eye, neoplasm
Eye, neoplasm
(retinoblastoma, inhibitors; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Antitumor agents

(retinoblastoma; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Nose
(rhinitis; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Peritoneum
(septic peritonitis; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Antidiarrheals
Antipyretics
Antiviral agents
Behcet's syndrome
Cosmetics
Cytomegalovirus
Drug delivery systems
Encephalitis
Herpesviridae
Human herpesvirus
Human herpesvirus 1
Human herpesvirus 2
Human herpesvirus 3
Human herpesvirus 4
Human herpesvirus 5
Human herpesvirus 6
Human herpesvirus 8
Lymphoproliferative disorders
Mononucleosis
Nervous system agents
Sexually transmitted diseases
Skin, disease
Werner syndrome
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Peptides, biological studies
Sulfides, biological studies
Sulfoxides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Analgesics
Anesthetics
Antibiotics
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections, and use with other agents)
IT Drug delivery systems
(solns.; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Drug delivery systems
(topical; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Kidney
Kidney
(transplant, epithelial tumors associated with; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Drug delivery systems
(unit doses; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
IT Drug delivery systems

(vaginal; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Human herpesvirus 3
(varicella from, skin sores; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Hepatitis
(viral, herpetic; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Reproductive organ
Reproductive tract
(vulva, neoplasm, inhibitors; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT Antitumor agents
(vulva; serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT 37259-58-8, Serine protease
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT **9041-92-3**, α **1 Antitrypsin**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT 145852-04-6 145852-05-7 145852-06-8 145852-07-9 145852-08-0
145852-14-8 145852-15-9 180526-15-2 291296-75-8 291296-76-9
291296-77-0 291296-78-1 291296-79-2 291296-80-5 291296-81-6
291296-82-7 291296-83-8 291296-84-9 291296-85-0 291296-86-1
291296-87-2 291296-88-3 291296-89-4 291296-90-7 291296-91-8
291296-92-9 291296-93-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT 98-10-2D, Benzenesulfonamide, derivs. 289-06-5D, Thiadiazole, derivs. 11120-54-0D, Oxadiazole, derivs. 27988-97-2D, Tetrazole, derivs. 37306-44-8D, Triazole, peptoid derivs. 179752-50-2 179752-51-3
179752-52-4 179752-53-5 179752-54-6 179752-55-7 179752-56-8
179752-57-9 179752-58-0 179752-59-1 179752-60-4 179752-61-5
179752-62-6 179752-64-8 179752-65-9 208840-11-3 208840-12-4
208840-13-5 208840-14-6 208840-18-0 208840-19-1 208840-20-4
208840-21-5 208840-22-6 208840-24-8 208840-25-9 208840-27-1
208840-28-2 208840-39-5 208845-34-5 208845-35-6 208845-38-9
208845-39-0 208845-40-3 208845-43-6 208845-56-1 208845-62-9
208845-63-0 208845-65-2 208845-66-3 208845-77-6 208845-85-6
208846-02-0 208846-03-1 208846-13-3 208847-42-1 208847-55-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)

IT **9004-06-2**, Elastase 56645-49-9, Cathepsin G 128028-50-2, Proteinase-3 186322-81-6, Caspase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(serine protease inhibitors and methods and compns. for treatment of

herpes virus infections)
IT 292094-96-3
RL: PRP (Properties)
(unclaimed protein sequence; inhibitors of serine protease activity, and methods and compns. for treatment of herpes virus infections)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Cortech; WO 9824806 A 1998 HCAPLUS
(2) Emory University; WO 9846597 A 1998 HCAPLUS
(3) Lezdey, J; WO 9407525 A 1994 HCAPLUS
IT **9041-92-3**, α **1 Antitrypsin**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9004-06-2**, Elastase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(serine protease inhibitors and methods and compns. for treatment of herpes virus infections)
RN 9004-06-2 HCAPLUS
CN Elastase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2000:628008** HCAPLUS
DN **133:217724**
ED Entered STN: 10 Sep 2000
TI Inhibitors of serine protease activity, and methods and compositions for treatment of nitric oxide-induced clinical conditions
IN Shapiro, Leland
PA The Trustees of University Technology Corp., USA
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-00
CC 1-12 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000051623	A2	20000908	WO 2000-US5556	20000303 <--
WO 2000051623	A3	20001214		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6489308	B1	20021203	US 2000-518097	20000303 <--

PRAI US 1999-123167P P 19990305 <--
US 1999-156523P P 19990929 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000051623	ICM	A61K038-00
WO 2000051623	ECLA	A61K038/08; A61K038/57 <--
US 6489308	NCL	514/045.000; 514/423.000; 514/454.000; 514/613.000
	ECLA	A61K038/57+M <--

AB A method of treating and preventing diseases is provided. In particular, compns. and methods of blocking diseases associated with aberrant levels of nitric oxide and facilitated by a serine proteolytic activity are disclosed, which consist of administering to a subject a therapeutically effective amount of a compound having a serine protease inhibitory activity. Among effective compds. are **.alpha.1-antitrypsin** and synthetic drugs mimicking some or all of the actions of **.alpha.1-antitrypsin.**

ST serine protease inhibitor NO assocd disease; nitric oxide assocd disease serine protease inhibitor; alpha1 antitrypsin NO assocd disease treatment

IT Intestine, disease
(Hirschsprung's disease; serine protease inhibitors for treatment of NO-induced diseases)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NF-κB (nuclear factor κB); serine protease inhibitors for treatment of NO-induced diseases)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PAR (proteinase-activated receptors), inhibitors; serine protease inhibitors for treatment of NO-induced diseases)

IT Pancreas, disease
(acute pancreatitis; serine protease inhibitors for treatment of NO-induced diseases)

IT Respiratory distress syndrome
(adult; serine protease inhibitors for treatment of NO-induced diseases)

IT Aging, animal
(age-associated memory impairment; serine protease inhibitors for treatment of NO-induced diseases)

IT Nervous system
(amyotrophic lateral sclerosis; serine protease inhibitors for treatment of NO-induced diseases)

IT Artery
(angioplasty; serine protease inhibitors for treatment of NO-induced diseases)

IT Antiarteriosclerotics
(antiatherosclerotics; serine protease inhibitors for treatment of NO-induced diseases)

IT Heart, disease
(autoimmune myocarditis; serine protease inhibitors for treatment of NO-induced diseases)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blocking; serine protease inhibitors for treatment of NO-induced diseases)

IT Drug delivery systems
(buccal; serine protease inhibitors for treatment of NO-induced

diseases)
IT Development, mammalian postnatal
(child, pediatric respiratory failure; serine protease inhibitors for treatment of NO-induced diseases)
IT Lung, disease
(chronic obstructive; serine protease inhibitors for treatment of NO-induced diseases)
IT Liver, disease
Lung, disease
(chronic; serine protease inhibitors for treatment of NO-induced diseases)
IT Artery
(coronary, ectasia; serine protease inhibitors for treatment of NO-induced diseases)
IT Artery, disease
(coronary; serine protease inhibitors for treatment of NO-induced diseases)
IT Nervous system
(degeneration; serine protease inhibitors for treatment of NO-induced diseases)
IT Nerve, disease
(diabetic neuropathy; serine protease inhibitors for treatment of NO-induced diseases)
IT Uterus, disease
(dysfunctional bleeding; serine protease inhibitors for treatment of NO-induced diseases)
IT Kidney, disease
(end-stage; serine protease inhibitors for treatment of NO-induced diseases)
IT Drug delivery systems
(epidural; serine protease inhibitors for treatment of NO-induced diseases)
IT Heart, disease
(failure; serine protease inhibitors for treatment of NO-induced diseases)
IT Stomach, disease
(gastritis; serine protease inhibitors for treatment of NO-induced diseases)
IT Drugs
(gastrointestinal; serine protease inhibitors for treatment of NO-induced diseases)
IT Stress, animal
(heat; serine protease inhibitors for treatment of NO-induced diseases)
IT Hypoxia, animal
(hypoxemia, hypoxemic respiratory failure; serine protease inhibitors for treatment of NO-induced diseases)
IT Heart, disease
(infarction; serine protease inhibitors for treatment of NO-induced diseases)
IT Joint, anatomical
Respiratory tract
(inflammation; serine protease inhibitors for treatment of NO-induced diseases)
IT Intestine, disease
(inflammatory; serine protease inhibitors for treatment of NO-induced diseases)
IT Stomach, neoplasm
Stomach, neoplasm
(inhibitors; serine protease inhibitors for treatment of NO-induced diseases)

IT Drug delivery systems
(injections, i.m.; serine protease inhibitors for treatment of NO-induced diseases)
IT Drug delivery systems
(injections, i.v.; serine protease inhibitors for treatment of NO-induced diseases)
IT Drug delivery systems
(injections, s.c.; serine protease inhibitors for treatment of NO-induced diseases)
IT Reperfusion
(injury; serine protease inhibitors for treatment of NO-induced diseases)
IT Drug delivery systems
(intracerebrovascular; serine protease inhibitors for treatment of NO-induced diseases)
IT Drug delivery systems
(intrathecal; serine protease inhibitors for treatment of NO-induced diseases)
IT Brain, disease
Heart, disease
Kidney, disease
Liver, disease
Lung, disease
(ischemia; serine protease inhibitors for treatment of NO-induced diseases)
IT Apparatus
(mech. device for reestablishment of blood flow; serine protease inhibitors for treatment of NO-induced diseases)
IT Circulation
(mech. device for reestablishment of; serine protease inhibitors for treatment of NO-induced diseases)
IT Drug delivery systems
(nasal; serine protease inhibitors for treatment of NO-induced diseases)
IT Newborn
(neonatal respiratory failure; serine protease inhibitors for treatment of NO-induced diseases)
IT Toxicity
(nephrotoxicity; serine protease inhibitors for treatment of NO-induced diseases)
IT cDNA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(of inhibitory kinases; serine protease inhibitors for treatment of NO-induced diseases)
IT Drug delivery systems
(oral; serine protease inhibitors for treatment of NO-induced diseases)
IT Drug delivery systems
(osmotic pumps; serine protease inhibitors for treatment of NO-induced diseases)
IT **Ear**
(**otitis, otitis media**, chronic; serine protease inhibitors for treatment of NO-induced **diseases**)
IT Drug delivery systems
(parenterals; serine protease inhibitors for treatment of NO-induced diseases)
IT Antioxidants
(pharmaceutical; serine protease inhibitors for treatment of NO-induced diseases)

IT Pleura
(pleurisy; serine protease inhibitors for treatment of NO-induced diseases)
IT Fatty acids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyunsatd., omega-3, and complexes; serine protease inhibitors for treatment of NO-induced diseases)
IT Fatty acids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyunsatd., omega-6, and complexes; serine protease inhibitors for treatment of NO-induced diseases)
IT Disease, animal
(primary ciliary dyskinesia; serine protease inhibitors for treatment of NO-induced diseases)
IT Antihypertensives
(pulmonary; serine protease inhibitors for treatment of NO-induced diseases)
IT Drug delivery systems
(rectal; serine protease inhibitors for treatment of NO-induced diseases)
IT Breathing (animal)
(respiratory failure, acute; serine protease inhibitors for treatment of NO-induced diseases)
IT Eye, disease
(retinopathy; serine protease inhibitors for treatment of NO-induced diseases)
IT Shock (circulatory collapse)
(septic; serine protease inhibitors for treatment of NO-induced diseases)
IT Animal tissue culture
Anti-AIDS agents
Anti-Alzheimer's agents
Anti-inflammatory agents
Anti-ischemic agents
Antiarthritics
Antiasthmatics
Antidiabetic agents
Antiglaucoma agents
Antihypertensives
Antimalarials
Antimigraine agents
Antiparkinsonian agents
Antirheumatic agents
Antitumor agents
Antiviral agents
Autoimmune disease
Blood vessel, disease
Bone, disease
Cardiovascular agents
Cirrhosis
Cognition enhancers
Cytomegalovirus
Dysmenorrhea
Human herpesvirus 1
Ischemia
Liver, disease

Lung, disease
Lyme disease
Nervous system agents
Organ, animal
Oxidative stress, biological
Preeclampsia
Protozoacides
Radical scavengers
Sickle cell anemia
Thrombolytics
(serine protease inhibitors for treatment of NO-induced diseases)

IT Cytokines
Lipopolysaccharides
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(serine protease inhibitors for treatment of NO-induced diseases)

IT Hemoglobins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors for treatment of NO-induced diseases)

IT Myoglobins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors for treatment of NO-induced diseases)

IT Reactive oxygen species
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(serine protease inhibitors for treatment of NO-induced diseases)

IT Antitumor agents
Antitumor agents
(stomach; serine protease inhibitors for treatment of NO-induced diseases)

IT Brain, disease
(stroke; serine protease inhibitors for treatment of NO-induced diseases)

IT Lupus erythematosus
(systemic; serine protease inhibitors for treatment of NO-induced diseases)

IT Multiple sclerosis
(therapeutic agents; serine protease inhibitors for treatment of NO-induced diseases)

IT Kidney
(toxicity; serine protease inhibitors for treatment of NO-induced diseases)

IT Drug delivery systems
(transdermal; serine protease inhibitors for treatment of NO-induced diseases)

IT Brain, disease
(trauma; serine protease inhibitors for treatment of NO-induced diseases)

IT Kidney, disease
(tubulointerstitial, acquired; serine protease inhibitors for treatment of NO-induced diseases)

IT Drug delivery systems
(vaginal; serine protease inhibitors for treatment of NO-induced diseases)

IT Interferons

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(γ; serine protease inhibitors for treatment of NO-induced diseases)

IT Headache
('hot dog headache'; serine protease inhibitors for treatment of NO-induced diseases)

IT 56-86-0, L-Glutamic acid, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(glutamate-induced asthma and glutamate-induced Chinese restaurant syndrome; serine protease inhibitors for treatment of NO-induced diseases)

IT 289-06-5D, Thiadiazole, derivs. 11120-54-0D, Oxadiazole, derivs. 37306-44-8D, Triazole, peptoid derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; serine protease inhibitors for treatment of NO-induced diseases)

IT **9004-06-2**, Elastase 125978-95-2, Nitric oxide synthase 128028-50-2, Proteinase-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; serine protease inhibitors for treatment of NO-induced diseases)

IT 9001-92-7, Protease 9031-44-1, Kinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitory; serine protease inhibitors for treatment of NO-induced diseases)

IT 50-81-7, Vitamin C, biological studies 50-81-7D, Vitamin C, complexes 52-90-4, Cysteine, biological studies 52-90-4D, Cysteine, complexes 55-63-0, Nitroglycerine 56-06-4, 2,4-Diamino-6-hydroxypyrimidine 71-44-3, Spermine 79-17-4, Aminoguanidine 100-33-4 124-20-9, Spermidine 140-64-7, Pentamidine isethionate 151-16-6 298-83-9, p-Nitroblue tetrazolium chloride 432-70-2, α-Carotene 432-70-2D, α-Carotene, complexes 458-37-7, Curcumin 458-37-7D, Curcumin, complexes 616-91-1, N-Acetylcysteine 616-91-1D, N-Acetylcysteine, complexes 867-44-7 1071-37-0, 2-Ethyl-2-thiopseudourea hydrobromide 1190-74-5, Mercaptoethylguanidine 1406-18-4, Vitamin E 1406-18-4D, Vitamin E, complexes 2149-70-4 2751-09-9, Troleandomycin 2942-42-9, 7-Nitroindazole 2986-19-8, S-Methylisothiourea 2986-20-1, S-Ethylisothiourea 4673-26-1 7235-40-7, β-Carotene 7235-40-7D, β-Carotene, complexes 7782-49-2, Selenium, biological studies 7782-49-2D, Selenium, complexes, biological studies 8001-27-2, Hirudin **9041-92-3**, α **1-Antitrypsin** 9054-89-1, Superoxide dismutase 9054-89-1D, Superoxide dismutase, complexes 11103-57-4, Vitamin A 11103-57-4D, Vitamin A, complexes 13395-35-2, 2-Iminobiotin 17035-90-4 18144-22-4 20933-81-7 21835-19-8 22722-03-8, S-Ethylisothiourea sulfate 25769-03-3, 1-Pyrrolidinecarbodithioic acid 30344-00-4 33876-97-0 36889-13-1 50912-92-0 53774-63-3 57564-91-7, S-Nitroso-glutathione 66036-77-9, NG-Nitro-D-arginine 74209-34-0, 3-Bromo-7-nitroindazole 75830-53-4 79032-48-7, S-Nitroso-N-acetylpenicillamine 112229-23-9 133587-00-5, NG-Monomethyl-L-arginine acetate 137694-74-7 150403-88-6 156719-37-8, L-Thiocitrulline 156719-41-4, S-Methyl-L-thiocitrulline 179752-50-2 179752-51-3 179752-52-4 179752-53-5 179752-54-6

179752-55-7 179752-56-8 179752-57-9 179752-58-0 179752-59-1
179752-60-4 179752-61-5 179752-62-6 179752-64-8 179752-65-9
208840-11-3 208840-12-4 208840-13-5 208840-14-6 208840-18-0
208840-19-1 208840-20-4 208840-21-5 208840-22-6 208840-24-8
208840-25-9 208840-27-1 208840-28-2 208840-39-5 208845-34-5
208845-35-6 208845-38-9 208845-39-0 208845-40-3 208845-43-6
208845-56-1 208845-62-9 208845-63-0 208845-65-2 208845-66-3
208845-77-6 208845-85-6 208846-02-0 208846-03-1 208846-13-3
208847-42-1 208847-55-6 209248-80-6 209248-86-2 209589-59-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors for treatment of NO-induced diseases)
IT 7782-44-7D, Oxygen, reactive species, biological studies 10102-43-9, Nitric oxide, biological studies 137632-07-6, p44 MAP kinase 137632-08-7, p42 MAP kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(serine protease inhibitors for treatment of NO-induced diseases)
IT 292094-95-2
RL: PRP (Properties)
(unclaimed protein sequence; inhibitors of serine protease activity, and methods and compns. for treatment of nitric oxide-induced clin. conditions)
IT **9004-06-2**, Elastase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; serine protease inhibitors for treatment of NO-induced diseases)
RN 9004-06-2 HCAPLUS
CN Elastase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9041-92-3**, α **1-Antitrypsin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serine protease inhibitors for treatment of NO-induced diseases)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1994:587340** HCAPLUS
DN **121:187340**
ED Entered STN: 15 Oct 1994
TI Treatment of inflammation with serine protease inhibitors
IN Lezdey, John; Wachter, Allan
PA USA
SO U.S., 4 pp. Cont.-in-part of U.S. 5,217,951.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K037-64
INCL 514008000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 6

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	US 5290762	A	19940301	US 1993-18888	19930217 <--
	US 5008242	A	19910416	US 1989-445005	19891204 <--
	CA 2019974	AA	19910604	CA 1990-2019974	19900627 <--
	CA 2019974	C	20020122		
	EP 432117	A1	19910612	EP 1990-850286	19900829 <--
	EP 432117	B1	19940622		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	ES 2055406	T3	19940816	ES 1990-850286	19900829 <--
	JP 03181422	A2	19910807	JP 1990-238844	19900906 <--
	US 5114917	A	19920519	US 1990-591630	19901002 <--
	US 5166134	A	19921124	US 1991-710055	19910604 <--
	US 5217951	A	19930608	US 1991-781003	19911018 <--
PRAI	US 1986-946445	B2	19861224 <--		
	US 1988-181707	A2	19880414 <--		
	US 1988-242735	B2	19880909 <--		
	US 1989-445005	A2	19891204 <--		
	US 1990-591630	A2	19901002 <--		
	US 1990-598241	B2	19901016 <--		
	US 1991-643727	B2	19910118 <--		
	US 1991-781003	A2	19911018 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5290762	ICM	A61K037-64
	INCL	514008000
US 5290762	NCL	514/008.000; 514/002.000; 514/012.000; 514/021.000 <--
US 5008242	NCL	514/008.000; 514/021.000; 530/380.000; 530/395.000; 530/397.000 <--
EP 432117	ECLA	A61K009/127; A61K038/57 <--
US 5114917	NCL	514/008.000; 514/002.000; 514/012.000; 514/021.000; 530/397.000 <--
US 5166134	NCL	514/008.000; 514/002.000; 514/012.000; 514/021.000 <--
US 5217951	NCL	514/008.000; 514/002.000; 514/021.000; 530/395.000 <--

AB A method for the prophylaxis or direct treatment of inflammatory diseases or injuries comprises administering to the site of the disease or injury an effective amount of at least one serine protease inhibitor, its salts, derivs. or analogs which bind with the mast cell mediators, T-cell mediators or kallikrein. For example, a topical cream contained α-2 macroglobulin 1.0, olive oil 5.0, cetanol 2.0, stearic acid 5.0, glyceride 12.0, Tween-60 0.5, propylene glycol 0.5, methylparaben 0.1, propylparaben 0.02, and purified water to 100 g.

ST antiinflammatory serine protease inhibitor topical prepn

IT Mast cell
(mediators; treatment of inflammation with serine protease inhibitors)

IT Antihistaminics
Basophil
Eosinophil
Neutrophil
Psoriasis
Virucides and Virustats
(treatment of inflammation with serine protease inhibitors)

IT Kinins (animal hormones)
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(treatment of inflammation with serine protease inhibitors)

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C-reactive, treatment of inflammation with serine protease inhibitors)

IT Immunoglobulins
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(E, treatment of inflammation with serine protease inhibitors)
IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SAA (serum amyloid A), treatment of inflammation with serine protease inhibitors)
IT Lymphocyte
(T-cell, mediators; treatment of inflammation with serine protease inhibitors)
IT **Ear**
(**disease**, **otitis**, treatment of inflammation with serine protease inhibitors)
IT Eye, disease
(inflammation, treatment of inflammation with serine protease inhibitors)
IT Pharmaceutical dosage forms
(ointments, treatment of inflammation with serine protease inhibitors)
IT Pharmaceutical dosage forms
(ointments, creams, treatment of inflammation with serine protease inhibitors)
IT Pharmaceutical dosage forms
(solns., treatment of inflammation with serine protease inhibitors)
IT Macroglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α2-, treatment of inflammation with serine protease inhibitors)
IT 122320-05-2, Secretory leukocyte protease inhibitor 138757-15-0
139691-92-2, Serine protease inhibitor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of inflammation with serine protease inhibitors)
IT **9004-06-2**, Elastase 56645-49-9, Cathepsin G
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(treatment of inflammation with serine protease inhibitors)
IT **9004-06-2**, Elastase
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(treatment of inflammation with serine protease inhibitors)
RN 9004-06-2 HCAPLUS
CN Elastase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1992:123636** HCAPLUS
DN **116:123636**
ED Entered STN: 03 Apr 1992
TI ELISA to determine immunoreactive Pseudomonas aeruginosa elastase in chronic suppurative **otitis media**
AU Jin, Chun Shun; Hamaguchi, Yukiyoshi; Sakakura, Yasuo
CS Sch. Med., Mie Univ., Tsu, 514, Japan
SO International Archives of Allergy and Applied Immunology (**1991**), 96(3), 193-8

CODEN: IAAAAM; ISSN: 0020-5915
DT Journal
LA English
CC 7-1 (Enzymes)
Section cross-reference(s): 14
AB A sensitive sandwich ELISA was developed to measure the levels of P. aeruginosa elastase (PE) in ear discharges from chronic suppurative **otitis media** (CSOM) patients. Preincubation of the sample with EDTA before ELISA was employed to inhibit PE activity which hydrolyzes the anti-PE IgG antibody into a smaller mol. form. The PE levels of 10 middle ear effusions (MEE) from chronic **otitis media** with effusion were also measured. In CSOM, 9 of 10 samples had significant PE levels, ranging from 6.8 to 62.1 μg/mL, which were significantly higher than those in MEE, the majority of which was below the detection limit. Two samples of CSOM with the P. aeruginosa infection showed high PE levels. This sandwich ELISA for the measurement of PE is a very sensitive method requiring only a small sample amount
ST elastase Pseudomonas detn ELISA **otitis media**
IT Pseudomonas aeruginosa
(elastase of, determination of immunoreactive, in ear discharges of humans with
chronic suppurative **otitis media**, ELISA for)
IT **Ear**
(**disease**, **otitis media**, elastase of Pseudomonas aeruginosa in ear discharges of humans with chronic suppurative, ELISA for determination of immunoreactive)
IT **9004-06-2**, Elastase
RL: ANST (Analytical study)
(determination of immunoreactive, of Pseudomonas aeruginosa in ear discharges
of humans with chronic suppurative **otitis media**, ELISA for)
IT **9004-06-2**, Elastase
RL: ANST (Analytical study)
(determination of immunoreactive, of Pseudomonas aeruginosa in ear discharges
of humans with chronic suppurative **otitis media**, ELISA for)
RN 9004-06-2 HCAPLUS
CN Elastase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1991:245275** HCAPLUS
DN **114:245275**
ED Entered STN: 28 Jun 1991
TI Neutrophil elastase in ear discharges of chronic suppurative **otitis media**
AU Hamaguchi, Yukiyoshi; Jin, Chun Shun; Suzumura, Hidehisa; Sakakura, Yasuo
CS Sch. Med., Mie Univ., Tsu, 514, Japan
SO Ear Research Japan (**1990**), 21(1), 15-16
CODEN: ERJAEA; ISSN: 0288-9781
DT Journal
LA Japanese
CC 14-3 (Mammalian Pathological Biochemistry)
AB Neutrophil elastase (NE) levels in ear discharges from chronic suppurative **otitis media** (CSOM) patients were measured by ELISA. Levels of NE complexed with **.alpha.1-antitrypsin** were higher in CSOM than in middle ear effusions from

chronic **otitis media** with effusion (OME). Total NE levels in CSOM were significantly higher than in chronic OME.
ST suppurative **otitis media** pus neutrophil elastase
IT Neutrophil
(elastase of, α **1-antitrypsin** complexes with, in pus, in chronic suppurative **otitis media**, of humans)
IT Pus
(neutrophil elastase complexes with α **1-antitrypsin** in, in chronic suppurative **otitis media**, of humans)
IT **Ear**
(**disease**, **otitis media**, with effusion, neutrophil elastase complexes with α **1-antitrypsin** in, of humans)
IT **Ear**
(**disease**, suppurative **otitis media**, neutrophil elastase complexes with α **1-antitrypsin** in pus in, of humans)
IT **9004-06-2**, Elastase **9004-06-2D**, Elastase, α **1-antitrypsin** complexes
9041-92-3D, Trypsin, elastase complexes
RL: BIOL (Biological study)
(neutrophil, of pus, in chronic suppurative **otitis media**, of humans)
IT **9004-06-2**, Elastase **9004-06-2D**, Elastase, α **1-antitrypsin** complexes
9041-92-3D, Trypsin, elastase complexes
RL: BIOL (Biological study)
(neutrophil, of pus, in chronic suppurative **otitis media**, of humans)
RN 9004-06-2 HCAPLUS
CN Elastase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9004-06-2 HCAPLUS
CN Elastase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1990:16407** HCAPLUS
DN **112:16407**
ED Entered STN: 21 Jan 1990
TI Antiinflammatory effects of a corticosteroid and protease inhibitor agents on antigen-induced **otitis media** in chinchillas
AU Hamaguchi, Yukiyoshi; Sakakura, Yasuo; Juhn, Steven K.
CS Fac. Med., Mie Univ., Tsu, 514, Japan
SO Ear Research Japan (**1989**), 20(1), 165-6
CODEN: ERJAEA; ISSN: 0288-9781
DT Journal
LA Japanese
CC 2-4 (Mammalian Hormones)
Section cross-reference(s): 14
AB The effects of a glucocorticoid, triamcinolone acetate, and of a kallikrein inhibitor, aprotinin, were examined on levels of **.alpha**

.1-antitrypsin and total protein concentration in the middle ear fluid and on leukocyte infiltration into the middle ear fluid of chinchillas. These drugs were injected into the middle ear with an antigen, human serum albumin. Both vascular permeability and leukocyte infiltration were suppressed by treatment with triamcinolone acetate or aprotinin. Apparently the kallikrein-kinin sysytem is related to the early stage of antigen-induced **otitis media.**

ST corticosteroid protease inhibitor **otitis media**; inflammation inhibition corticosteroid aprotinin

IT Corticosteroids, biological studies
RL: BIOL (Biological study)
(ear **otitis media** treatment by protease inhibitor and)

IT Leukocyte
(infiltration of, in ear **otitis media**, corticosteroid and protease inhibitor suppression of)

IT **Inflammation**
(inhibition of, by corticosteroid and protease inhibitor, in ear **otitis media**)

IT Blood vessel, metabolism
(permeability of, in ear **otitis media**, corticosteroid and protease inhibitor in decrease of)

IT Kinins (animal hormones)
RL: BIOL (Biological study)
(-kallikrein system, in ear **otitis media** pathogenesis)

IT **Ear**
(**disease**, **otitis media**, treatment of, with corticosteroid and protease inhibitor)

IT Biological transport
(permeation, of blood vessels, in ear **otitis media**, corticosteroids and protease inhibitor decrease of)

IT 9087-70-1, Aprotinin
RL: BIOL (Biological study)
(ear **otitis media** treatment by corticosteroid and)

IT 67-78-7
RL: BIOL (Biological study)
(ear **otitis media** treatment by protease inhibitor and)

L77 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1989:452922** HCAPLUS
DN **111:52922**
ED Entered STN: 20 Aug 1989
TI Purification and properties of Streptococcus pneumoniae neuraminidase
AU Scanlon, K. Lenia; Diven, Warren F.; Glew, Robert H.
CS Sch. Med., Univ. Pittsburgh, Pittsburgh, PA, 15261, USA
SO Enzyme (**1989**), 41(3), 143-50
CODEN: ENZYBT; ISSN: 0013-9432
DT Journal
LA English
CC 7-2 (Enzymes)
AB To study the role of neuraminidase of S. pneumoniae in the pathol. of **otitis media** a method for its purification was developed. The enzyme was purified >5,800-fold by removing the organism and passing the culture broth through a series of affinity and ion-exchange columns. The overall yield was 2 mg enzyme protein and the final specific activity was 1.8 + 106 units/mg protein. A mol. weight of 65,000 was estimated by SDS-PAGE and gel-filtration chromatog. The Stokes radius of neuraminidase was calculated to be 32 Å, its isoelec. point was 7.2, and its pH optimum

was 6.0. In terms of specificity, the enzyme catalyzed the hydrolysis of sialic acid linkages in mucin, glycoproteins, and gangliosides: bovine submaxillary mucin supported the highest catalytic efficiency, and . **alpha.-1-antitrypsin** the lowest.
Neuraminidase acted on ≥3 linkage classes of substrates, α-2,6 and α-2,3 linkages of N-acetylneuraminic acid to galactose, and α-2,6 linkages to N-acetylgalactosamine.

ST neuraminidase Streptococcus; **otitis media**
neuraminidase Streptococcus

IT Streptococcus pneumoniae
(neuraminidase of, purification and properties of)

IT Michaelis constant
(of neuraminiase, of Streptococcus pneumoniae)

IT Fetuins
Transferrins
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with neuraminidase of Streptococcus pneumoniae, kinetics of)

IT Molecular structure-biological activity relationship
(neuraminidase substrate, of carbohydrates and gangliosides and glycoproteins)

IT Mucins
RL: RCT (Reactant); RACT (Reactant or reagent)
(sialo-, reaction of, with neuraminidase of Streptococcus pneumoniae, kinetics of)

IT 9001-67-6P, Neuraminidase
RL: PREP (Preparation)
(of Streptococcus pneumoniae, purification and properties of)

IT **9041-92-3**, α **1-Antitrypsin**
12707-58-3, Ganglioside GD1a 35890-38-1, Neuramin lactose 59322-44-0
93230-05-8, Ganglioside GT1
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with neuraminidase of Streptococcus pneumoniae, kinetics of)

IT **9041-92-3**, α **1-Antitrypsin**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with neuraminidase of Streptococcus pneumoniae, kinetics of)

RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1979:133539** HCAPLUS
DN **90:133539**
ED Entered STN: 12 May 1984
TI Alpha1-antitrypsin in the inner ear perilymph and other body fluids
AU Opolska, Barbara; Trela, Franciszek
CS Zakl. Med. Sadowej, Akad. Med., Krakow, Pol.
SO Folia Medica Cracoviensia (**1978**), 20(1), 135-7
CODEN: FMCRAW; ISSN: 0015-5616
DT Journal
LA Polish
CC 4-2 (Toxicology)
AB **.alpha.1-Antitrypsin** [**9041-92-3**]
was detected in 89.0% of inner ear perilymph and in 62.13% of the cerebrospinal fluid samples examined, but not in vitreous fluid. The samples were all taken from human cadavers. **.alpha.1-Antitrypsin** anal. may be useful in the identification of corpses.

ST antitrypsin body fluid forensic analysis
IT Legal chemistry and medicine
(antitrypsin detection in body fluids in)
IT Body fluid
(antitrypsin detection in, in forensic anal.)
IT Cerebrospinal fluid
(fluid of, antitrypsin detection in, in forensic anal.)
IT **Ear**
(labyrinth, fluid of, antitrypsin detection in, in forensic anal.)
IT **9041-92-3**
RL: BIOL (Biological study)
(of body fluids, forensic anal. in relation to)
IT **9041-92-3**
RL: BIOL (Biological study)
(of body fluids, forensic anal. in relation to)
RN 9041-92-3 HCAPLUS
CN Trypsin inhibitor, α1- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1977:403911** HCAPLUS
DN **87:3911**
ED Entered STN: 12 May 1984
TI Complement C3 proactivator as an acute phase reactant
AU Ota, Hisahiro
CS Nagasaki City Hosp., Nagasaki, Japan
SO Igaku no Ayumi (**1977**), 100(12), 866-8
CODEN: IGAYAY; ISSN: 0039-2359
DT Journal
LA Japanese
CC 15-13 (Immunochemistry)
AB The increased levels of serum C3 proactivator in infections (e.g. acute **otitis media**, leg abscess) approx. paralleled that of . **alpha.1-antitrypsin** and C-reactive protein.
ST complement C3 proactivator inflammation
IT Inflammation
(complement in)
IT Complement
(C3 proactivator, acute phase reactant activity of)

=> => fil medline
FILE 'MEDLINE' ENTERED AT 15:31:40 ON 21 JUN 2005

FILE LAST UPDATED: 18 JUN 2005 (20050618/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot

L113 ANSWER 1 OF 19 MEDLINE on STN
AN **2002258084** MEDLINE
DN PubMed ID: **11997781**
TI Inhibition of **matrix metalloproteinases** in gerbil cholesteatoma: preliminary findings.
AU Lehman David A; Wilmoth Jason G; Prevatt Angela R; Schultz Gregory S; Antonelli Patrick J
CS Department of Otolaryngology, University of Florida, Gainesville 32610-0264, USA.
SO Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery, **(2002 Apr)** 126 (4) 404-8.
Journal code: 8508176. ISSN: 0194-5998.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200206
ED Entered STN: 20020509
Last Updated on STN: 20020611
Entered Medline: 20020606
AB OBJECTIVES: This study was conducted to examine the role of **matrix metalloproteinases** (**MMPs**) and the impact of a topical **MMP** inhibitor, ilomostat, on the development of tympanic membrane (TM) atelectasis in the gerbil model. METHODS: Eustachian tubes were cauterized bilaterally in 19 gerbils. Thereafter, both TMs received once-daily topical treatment for 8 weeks with ilomostat or vehicle or no treatment (n = 6 or 7 per group). TM atelectasis was serially graded, and TMs were harvested at 8 weeks. Gelatin zymograms were performed to determine **MMP** activity. RESULTS: The mean activity levels of proenzyme and active **MMP**-9 and **MMP**-2 and degree of atelectasis did not differ between groups. TM atelectasis did not correlate to levels of enzymes across individual samples. CONCLUSIONS: Topical application of an **MMP** inhibitor did not significantly prevent the development of TM atelectasis. It remains to be determined whether the use of **MMP** inhibitors may prevent the progression of atelectasis in humans.
CT Check Tags: Male
Animals
***Cholesteatoma, Middle Ear: PC, prevention & control**
*Dipeptides: TU, therapeutic use
Gelatinase A: ME, metabolism
Gelatinase B: ME, metabolism
Gerbillinae
***Matrix Metalloproteinases: AI, antagonists & inhibitors**
***Matrix Metalloproteinases: PH, physiology**
*Protease Inhibitors: TU, therapeutic use
Tympanic Membrane: DE, drug effects
CN 0 (Dipeptides); 0 (**GM 6001**); 0 (Protease Inhibitors); EC 3.4.24.- (**Matrix Metalloproteinases**); EC 3.4.24.24 (Gelatinase A); EC 3.4.24.35 (Gelatinase B)

L113 ANSWER 2 OF 19 MEDLINE on STN
AN **2002110540** MEDLINE
DN PubMed ID: **11843930**

TI **Matrix metalloproteinases** 2 and 9 in otitis media with effusion.
AU Jennings C R; Guo L; Collins H M; Birchall J P
CS Department of Otorhinolaryngology and Head and Neck Surgery, Queen's Medical Centre, University Hospital, Nottingham, UK.
SO Clinical otolaryngology and allied sciences, **(2001 Dec)** 26 (6) 491-4.
Journal code: 7701793. ISSN: 0307-7772.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200203
ED Entered STN: 20020215
Last Updated on STN: 20020314
Entered Medline: 20020313
AB A qualitative and quantitative study of the presence of **matrix metalloproteinase** 2 (**MMP** 2) and **matrix metalloproteinase** 9 (**MMP** 9), in the effusions of otitis media with effusion (OME), was performed. The activity of the above enzymes was compared in thick and thin effusions, and concentrations compared in samples from children with one, two, three and four sets of ventilation tubes. The activity of both **MMP** 2 and **MMP** 9 was higher in thick than thin effusions, P = 0.07 and P = 0.04, respectively. The concentrations of **MMP** 9 did not vary with the number of tube insertions but those of **MMP** 2 did (ANOVA P < 0.05). **MMPs** may be involved in tympanic membrane damage and prognosis of OME.
CT Check Tags: Female; Male
Child
Child, Preschool
Electrophoresis, Agar Gel
Enzyme-Linked Immunosorbent Assay
*Exudates and Transudates: EN, enzymology
***Gelatinase A: ME, metabolism**
***Gelatinase B: ME, metabolism**
Humans
Middle Ear Ventilation
***Otitis Media with Effusion: EN, enzymology**
Otitis Media with Effusion: SU, surgery
Research Support, Non-U.S. Gov't
Viscosity
CN EC 3.4.24.24 (Gelatinase A); EC 3.4.24.35 (Gelatinase B)

L113 ANSWER 3 OF 19 MEDLINE on STN
AN **1998453249** MEDLINE
DN PubMed ID: **9781988**
TI Analysis of protease activity in human otitis media.
AU Avidano M A; Cotter C S; Stringer S P; Schultz G S
CS Department of Otolaryngology-Head and Neck Surgery, University of Florida College of Medicine, Gainesville, USA.
SO Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery, **(1998 Oct)** 119 (4) 346-51.
Journal code: 8508176. ISSN: 0194-5998.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199811

ED Entered STN: 19990106
Last Updated on STN: 20000303
Entered Medline: 19981103

AB Chronic otitis media is a common problem associated with a nonintact tympanic membrane frequently involving Staphylococcus aureus and Pseudomonas aeruginosa. The virulence of Pseudomonas bacteria is related to the production of two **matrix metalloproteinases**, elastase and alkaline **protease.** Serine **proteases**, such as neutrophil elastase, are produced by the host inflammatory response. These **proteases** are thought to contribute to tissue destruction and assist bacterial invasion during infection. This preliminary study was done to identify **protease** activity in otorrhea samples from patients with otitis media and a nonintact tympanic membrane and to examine the ability of selective **protease** inhibitors to decrease **protease** activity. Ilomostat (**galardin**) is a synthetic, specific inhibitor of **matrix metalloproteinases** including P. aeruginosa elastase and alkaline **protease**, whereas alpha1-antitrypsin inhibits serine **proteases** including neutrophil elastase. Samples were collected and cultured from 20 patients with otorrhea resulting from tympanic membrane perforations or pressure-equalization tubes. A **protease** assay that used azocasein as the substrate was used to quantify **protease** activity, with and without addition of selective **protease** inhibitors. Cultures revealed P. aeruginosa alone in 7 samples, P. aeruginosa plus other organisms in 10, and S. aureus alone in 3. **Protease** activity was detected in 15 (75%) of the samples. A statistically significant ($p < 0.05$) decrease in **protease** activity was seen with the addition of alpha1-antitrypsin or Ilomostat plus alpha1-antitrypsin, but not with Ilomostat alone. Analyzing the 10 samples with the highest **protease** activity, a statistically significant decrease in activity was seen with Ilomostat or alpha1-antitrypsin alone and with both Ilomostat and alpha1-antitrypsin together. Bacteriologic type, source of sample, age and gender of the subject, and duration of infection were not significantly related to **protease** activity. This is the first study to quantify **protease** activity and inhibition by selective **protease** inhibitors in human otorrhea. **Protease** inhibitors effectively decrease **protease** activity in most cases and in addition to standard antibiotic therapy might prove beneficial in the treatment of otitis media with a nonintact tympanic membrane. This study supports future clinical investigations into the role of **proteases** and inhibition of **protease** activity in the treatment of otitis media.

CT Check Tags: Female; Male
Anti-Bacterial Agents: TU, therapeutic use
Bacterial Proteins: AN, analysis
Bacterial Proteins: AI, antagonists & inhibitors
Bacterial Proteins: BI, biosynthesis
Caseins: DU, diagnostic use
Child
Child, Preschool
Chronic Disease
Dipeptides: PD, pharmacology
*Endopeptidases: AN, analysis
Humans
Leukocyte Elastase: AN, analysis
Leukocyte Elastase: AI, antagonists & inhibitors
Leukocyte Elastase: BI, biosynthesis
*Membrane Transport Proteins
Metalloendopeptidases: AN, analysis

Metalloendopeptidases: AI, antagonists & inhibitors
Metalloendopeptidases: BI, biosynthesis
Middle Ear Ventilation
Otitis Media: DT, drug therapy
***Otitis Media: EN, enzymology**
Otitis Media: MI, microbiology
Pancreatic Elastase: AN, analysis
Pancreatic Elastase: AI, antagonists & inhibitors
Pancreatic Elastase: BI, biosynthesis
Protease Inhibitors: PD, pharmacology
Protease Inhibitors: TU, therapeutic use
Pseudomonas Infections: DT, drug therapy
Pseudomonas Infections: EN, enzymology
Pseudomonas aeruginosa: EN, enzymology
Pseudomonas aeruginosa: PY, pathogenicity
Serine Endopeptidases: AN, analysis
Serine Endopeptidases: BI, biosynthesis
Serine Proteinase Inhibitors: PD, pharmacology
Staphylococcal Infections: DT, drug therapy
Staphylococcal Infections: EN, enzymology
Subtilisins: AN, analysis
Subtilisins: AI, antagonists & inhibitors
Subtilisins: BI, biosynthesis
Tympanic Membrane Perforation: EN, enzymology
Virulence
alpha 1-Antitrypsin: PD, pharmacology

CN 0 (Anti-Bacterial Agents); 0 (AprE protein, Bacteria); 0 (Bacterial Proteins); 0 (Caseins); 0 (Dipeptides); 0 (**GM 6001**); 0 (Membrane Transport Proteins); 0 (Protease Inhibitors); 0 (Serine Proteinase Inhibitors); 0 (**alpha 1-Antitrypsin**); 0 (azocasein); EC 3.4.- (Endopeptidases); EC 3.4.21 (Serine Endopeptidases); EC 3.4.21.- (Subtilisins); EC 3.4.21.36 (Pancreatic Elastase); EC 3.4.21.37 (Leukocyte Elastase); EC 3.4.24 (Metalloendopeptidases)

L113 ANSWER 4 OF 19 MEDLINE on STN
AN 1998319699 MEDLINE
DN PubMed ID: 9657594
TI Psychological change over 54 months of cochlear implant use.
AU Knutson J F; Murray K T; Husarek S; Westerhouse K; Woodworth G; Gantz B J; Tyler R S
CS Department of Psychology, The University of Iowa, Iowa City 52242, USA.
NC 2 P50 DC 00242 (NIDCD)
RR00059 (NCRR)
SO Ear and hearing, **(1998 Jun)** 19 (3) 191-201.
Journal code: 8005585. ISSN: 0196-0202.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199810
ED Entered STN: 19981029
Last Updated on STN: 19981029
Entered Medline: 19981022
AB OBJECTIVE: To determine the long-term psychological outcome of postlingually deafened adults who received multichannel cochlear implants and to relate the psychological outcome to audiological outcome. DESIGN: Thirty-seven recipients of multichannel cochlear implants who participated in a prospective clinical trial completed psychological assessments before implantation and at regularly scheduled follow-ups through 54 mo of

implant use. Standardized measures of affect, social function, and personality were used, and scores on these measures were correlated with asymptotic scores on several audiological measures. RESULTS: Evidence of significant improvement on measures of loneliness, social anxiety, and distress were obtained within a year after implantation and throughout the duration of the follow-up period. For measures of assertiveness and marital satisfaction, improvement was apparent only after long-term implant use. Although favorable changes on the Minnesota Multiphasic Personality Inventory (**MMPI**) Depression Scale were evidenced only in the initial follow-up period, improvements on the **MMPI** Paranoia and Social Introversion Scales persisted throughout the 54 mo follow-up. CONCLUSION: Multichannel cochlear implant use is associated with long-term psychological benefit. Correlations between audiological outcome and psychological outcome, however, suggested that the relation between audiological benefit and psychological benefit is not simple.

CT Check Tags: Female; Male
Adult
Aged
***Cochlear Implantation**
***Deafness: PX, psychology**
***Deafness: SU, surgery**
Depression: DI, diagnosis
Follow-Up Studies
Humans
MMPI
Middle Aged
Prospective Studies
Research Support, U.S. Gov't, P.H.S.
Time Factors

L113 ANSWER 5 OF 19 MEDLINE on STN
AN **96047567** MEDLINE
DN PubMed ID: **7554333**
TI Neutrophil elastase-**alpha 1-antitrypsin** in middle ear fluid in chronic otitis media with effusion.
AU Tierney P; Chan B; Samuel D; Thomas M; Patel K
CS Department of Otolaryngology-Head & Neck Surgery, St Mary's Hospital, London, UK.
SO Clinical otolaryngology and allied sciences, **(1995 Jun)** 20 (3) 230-3.
Journal code: 7701793. ISSN: 0307-7772.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199511
ED Entered STN: 19951227
Last Updated on STN: 20000303
Entered Medline: 19951114
AB Neutrophil elastase-**alpha 1-antitrypsin** was quantified in samples taken from middle ear effusions collected at operation from 17 children attending for elective myringotomy and grommet insertion. At the time of surgery the effusion was classified as serous or mucoid. Children with a recent history of infection or antimicrobial therapy were excluded. The quantification of immunoreactive neutrophil elastase was by means of enzyme-linked immunosorbant assay (ELISA). The mean value of neutrophil elastase-**alpha 1-antitrypsin** was 50.6 +/- 38.3 (SD) micrograms/ml in mucoid effusions, which was significantly higher ($P < 0.05$) than that in serous effusions (5.3 +/- 4.8 micrograms/ml). These results indicate that a

mucoid effusion may reflect a more severe inflammatory response and that persistence of neutrophil activity in the middle ear mucosa may contribute to the persistence of at least one group of middle ear effusions.

CT Child
Child, Preschool
Chronic Disease
***Ear, Middle: EN, enzymology**
***Ear, Middle: PP, physiopathology**
Enzyme-Linked Immunosorbent Assay
Humans
*Leukocyte Elastase: AN, analysis
Middle Ear Ventilation
*Neutrophils: CH, chemistry
***Otitis Media with Effusion: PP, physiopathology**
Otitis Media with Effusion: TH, therapy
*Pancreatic Elastase: AN, analysis
***alpha 1-Antitrypsin: AN, analysis**

CN 0 (**alpha 1-Antitrypsin**); EC 3.4.21.36 (Pancreatic Elastase); EC 3.4.21.37 (Leukocyte Elastase)

L113 ANSWER 6 OF 19 MEDLINE on STN
AN **94234651** MEDLINE
DN PubMed ID: **8179269**
TI Determining otitis media severity from middle ear fluid analysis.
AU Juhn S K; Garvis W J; Lees C J; Le C T; Kim C S
CS Otitis Media Research Center, University of Minnesota School of Medicine, Minneapolis.
NC P01-DC00133 (NIDCD)
SO Annals of otology, rhinology & laryngology. Supplement, **(1994 May)** 163 43-5.
Journal code: 1256156. ISSN: 0096-8056.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199406
ED Entered STN: 19940620
Last Updated on STN: 19940620
Entered Medline: 19940609
AB Otitis media has a complex multifactorial pathogenesis, and the middle ear inflammatory response is typified by the accumulation of cellular and chemical mediators in middle ear effusion. However, specific biochemical and immunochemical factors that may be responsible for the severity or chronicity of otitis media have not been identified. Identification of factors involved in chronicity appears to be an essential step in the treatment and ultimate prevention of chronic otitis media. We analyzed 70 effusion samples from patients 1 to 10 years of age who had chronic otitis media with effusion for two cytokines (interleukin-1 beta and tumor necrosis factor alpha) and total collagenase. The highest concentrations of all three inflammatory mediators were found in purulent otitis media, and concentrations were higher in younger than in older patients. Mediator concentrations were similar in samples obtained from patients having their first myringotomy for otitis media with effusion and in those who had had multiple previous myringotomies. The multiresponse star, which incorporates several biochemical parameters in one graphic illustration, may best characterize the complex nature of middle ear inflammation.
CT Child
Child, Preschool
Chronic Disease

***Collagenases: AN, analysis**
Collagenases: ME, metabolism
***Ear, Middle: CH, chemistry**
Ear, Middle: EN, enzymology
Ear, Middle: IM, immunology
*Exudates and Transudates: CH, chemistry
Humans
Infant
*Interleukin-1: AN, analysis
Interleukin-1: IM, immunology
***Otitis Media with Effusion: DI, diagnosis**
Otitis Media with Effusion: IM, immunology
Otitis Media with Effusion: PP, physiopathology
Research Support, U.S. Gov't, P.H.S.
*Tumor Necrosis Factor-alpha: AN, analysis
Tumor Necrosis Factor-alpha: IM, immunology
Tympanic Membrane: SU, surgery
CN 0 (Interleukin-1); 0 (Tumor Necrosis Factor-alpha); EC 3.4.24.- (Collagenases)

L113 ANSWER 7 OF 19 MEDLINE on STN
AN **93037039** MEDLINE
DN PubMed ID: **1416649**
TI Neutrophil elastase and its complex with **alpha 1-antitrypsin** in the pathogenesis of chronic suppurative otitis media.
AU Hamaguchi Y; Sakakura Y
CS Department of Otorhinolaryngology, Mie University School of Medicine, Tsu, Japan.
SO Annals of otology, rhinology & laryngology. Supplement, **(1992 Oct)** 157 26-31.
Journal code: 1256156. ISSN: 0096-8056.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199211
ED Entered STN: 19930122
Last Updated on STN: 20000303
Entered Medline: 19921119
AB Neutrophil elastase (NE) and its complex with **alpha 1-antitrypsin** were quantified in ear discharges from 15 patients with chronic suppurative otitis media (CSOM), and their levels were compared to those in middle ear effusions from 10 pediatric patients with chronic otitis media with effusion (OME). The localization of immunoreactive NE was also examined by immunocytologic study. The mean value of total NE was 161.8 +/- 29.5 micrograms/mL in CSOM, which was significantly higher than that in OME (16.5 +/- 6.7 micrograms/mL). The mean value of NE-**alpha 1-antitrypsin** complex was 13.7 +/- 8.8 micrograms/mL in CSOM and 7.8 +/- 4.0 micrograms/mL in OME. There was no significant difference between culture-positive and culture-negative samples in CSOM. Immunoreactive NE could be observed in the neutrophils of ear discharges, and extracellular release of NE was also observed. Ear discharges in CSOM contain a considerable amount of uncomplexed NE, of which the level does not depend on active bacterial infections. Uncomplexed NE seems to play a role in the chronicity of CSOM.
CT Check Tags: Female; Male
Adolescent
Adult

Aged
Child
Chronic Disease
Exudates and Transudates: EN, enzymology
Exudates and Transudates: IM, immunology
Humans
Infant
Leukocyte Count
Leukocyte Elastase
Middle Aged
Otitis Media with Effusion: EN, enzymology
Otitis Media with Effusion: IM, immunology
***Otitis Media, Suppurative: EN, enzymology**
Otitis Media, Suppurative: IM, immunology
*Pancreatic Elastase: ME, metabolism
Research Support, Non-U.S. Gov't
***alpha 1-Antitrypsin: ME, metabolism**
CN 0 (**alpha 1-Antitrypsin**); EC 3.4.21.36 (Pancreatic Elastase); EC 3.4.21.37 (Leukocyte Elastase)

L113 ANSWER 8 OF 19 MEDLINE on STN
AN **89298305** MEDLINE
DN PubMed ID: **2544990**
TI Microvascular response to locally injected collagenase. An experimental investigation in hamsters and rabbits.
AU Rydevik B; Ehira T; Linder L; Olmarker K; Romanus M; Branemark P I
CS Department of Orthopaedics, Gothenburg University, Sweden.
SO Scandinavian journal of plastic and reconstructive surgery and hand surgery / Nordisk plastikkirurgisk forening [and] Nordisk klubb for handkirurgi, **(1989)** 23 (1) 17-21.
Journal code: 8707869. ISSN: 0284-4311.
CY Sweden
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198908
ED Entered STN: 19900309
Last Updated on STN: 19900309
Entered Medline: 19890803
AB Collagenase was injected into the ears of rabbits and the cheek-pouches of hamsters. The acute and long-term microvascular effects were studied by vital microscopy and microangiography. The enzyme was injected at three different concentrations: 120 units/ml, 600 units/ml and 3,000 units/ml. The medium (600 units/ml) and high (3,000 units/ml) concentrations induced effects on the microcirculation such as blood flow impairment and microbleedings. The magnitude of these effects was related to the concentration of the enzyme. Generally, these microvascular effects were of low magnitude as compared with other substances tested using the same experimental models.
CT Animals
Cheek: BS, blood supply
Cheek: DE, drug effects
Cicatrix
Ear, External: BS, blood supply
Ear, External: DE, drug effects
Hamsters
Injections, Subcutaneous
Mesocricetus
***Microbial Collagenase: AD, administration & dosage**
Microbial Collagenase: PD, pharmacology

*Microcirculation: DE, drug effects
Rabbits
Regional Blood Flow
Research Support, Non-U.S. Gov't
CN EC 3.4.24.3 (Microbial Collagenase)

L113 ANSWER 9 OF 19 MEDLINE on STN
AN **89206052** MEDLINE
DN PubMed ID: **2468303**
TI Protease inhibitors in middle ear effusions from experimental otitis media with effusion: kinetics of **alpha 1-antitrypsin** and alpha 2-macroglobulin levels.
AU Hamaguchi Y; Juhn S K; Sakakura Y
CS Department of Otolaryngology, University of Minnesota, Minneapolis.
NC NS 14538 (NINDS)
SO Annals of otology, rhinology, and laryngology, **(1989 Apr)** 98 (4 Pt 1) 287-92.
Journal code: 0407300. ISSN: 0003-4894.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198905
ED Entered STN: 19900306
Last Updated on STN: 20000303
Entered Medline: 19890512
AB **Alpha 1-antitrypsin (alpha 1**-AT) and alpha 2-macroglobulin (alpha 2-M) were measured by both immunochemical and functional assays in paired plasma and middle ear effusions (MEEs) from experimental otitis media models (serous otitis media [SOM], purulent otitis media [POM], and SOM + POM). The MEE/plasma ratio of **alpha 1**-AT in SOM was significantly higher than that in POM (p less than .01) because of the high **alpha 1**-AT level in POM plasma. The ratio of both antitryptic activity and **trypsin**-binding activity in POM was significantly higher than that in SOM + POM (p less than .01, less than .05), and significantly lower than that in SOM (p less than .01). The majority of both **inhibitors** in SOM exists as the free state, and the reaction between proteases and **inhibitors** in POM and SOM + POM is more active than that in SOM. It is concluded that both **alpha 1**-AT and alpha 2-M appear to play an important role in the protection of middle ear mucosa by forming protease-**inhibitor** complexes to reduce proteolytic damage in POM and SOM + POM models.
CT Animals
Chinchilla
Disease Models, Animal
Ear, Middle: PP, physiopathology
Endopeptidases: ME, metabolism
Mucous Membrane: PP, physiopathology
***Otitis Media: PP, physiopathology**
***Otitis Media with Effusion: PP, physiopathology**
***Otitis Media, Suppurative: PP, physiopathology**
Research Support, U.S. Gov't, P.H.S.
***alpha 1-Antitrypsin: PK, pharmacokinetics**
*alpha-Macroglobulins: PK, pharmacokinetics
CN 0 (**alpha 1-Antitrypsin**); 0 (alpha-Macroglobulins); EC 3.4.- (Endopeptidases)

L113 ANSWER 10 OF 19 MEDLINE on STN
AN **89023753** MEDLINE

DN PubMed ID: **2459981**
TI Antiinflammatory effects of a corticosteroid and protease inhibitor agents on antigen-induced otitis media in chinchillas.
AU Hamaguchi Y; Juhn S K; Sakakura Y
CS Department of Otolaryngology, University of Minnesota Medical School, Minneapolis.
NC NS-14538 (NINDS)
SO American journal of otolaryngology, **(1988 May-Jun)** 9 (3) 142-8.
Journal code: 8000029. ISSN: 0196-0709.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198811
ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881115
AB Using an antigen-induced otitis media (OM) model in chinchillas sensitized with human serum albumin (HSA), we studied the antiinflammatory effect of a corticosteroid (triamcinolone) and a protease (kallikrein) inhibitor (aprotinin) by conducting both biochemical and cytologic analyses of middle ear fluid (MEF). The levels of HSA, **alpha 1-antitrypsin**, alpha 2-macroglobulin, and total protein concentration were measured in the MEF to evaluate the degree of OM. Both vascular leakage and leukocyte infiltration were significantly reduced by corticosteroid and inhibitor treatments. HSA levels in the MEF were markedly reduced after HSA challenge, and both treatments reduced the drop in HSA levels. In conclusion, the kallikrein-kinin system is related to the early stage of antigen-induced OM. Both corticosteroid and inhibitor treatments effectively reduce the degree of antigen-induced OM in chinchillas, suggesting that both may be useful local therapeutic agents in the treatment of human OM.
CT Animals
Aprotinin: ME, metabolism
*Aprotinin: TU, therapeutic use
Chinchilla
***Otitis Media with Effusion: DT, drug therapy**
Otitis Media with Effusion: ME, metabolism
Research Support, U.S. Gov't, P.H.S.
Serum Albumin: ME, metabolism
*Triamcinolone: TU, therapeutic use
alpha 1-Antitrypsin: ME, metabolism
alpha-Macroglobulins: ME, metabolism
RN 124-94-7 (Triamcinolone); 9087-70-1 (Aprotinin)
CN 0 (Serum Albumin); 0 (**alpha 1-Antitrypsin**);
0 (alpha-Macroglobulins)

L113 ANSWER 11 OF 19 MEDLINE on STN
AN **88268548** MEDLINE
DN PubMed ID: **2455499**
TI Biochemical and cytological studies of immune-complex-induced otitis media in the chinchilla.
AU Hamaguchi Y; Juhn S K; Sakakura Y
CS Department of Otolaryngology, University of Minnesota, Minneapolis 55414.
NC NS14538 (NINDS)
SO Archives of oto-rhino-laryngology, **(1988)** 245 (2) 77-81.
Journal code: 0414105. ISSN: 0302-9530.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 198808
ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880811
AB The pathogenesis of immune complex (IC)-induced otitis media in the chinchilla was studied through cytological and biochemical analyses of middle ear fluid (MEF) recovered after instillation of premade IC. The number to total leukocytes was 3.03 +/- 2.13 X 10(6)/cm3, and mainly involved neutrophils (72.3%) and macrophages (22.7%). The mean value of total protein, **alpha 1-antitrypsin** (**alpha 1**-AT) and alpha 2-macroglobulin (alpha 2-M) was 27.1 mg/ml, 189.5 and 75.2 mg/dl. The number of leukocytes had a significant correlation with the levels of total protein, **alpha 1**-AT and alpha 2-M (P less than 0.01). The inflammatory reaction induced by premade IC is characterized by an increased vascular leakage and an infiltration of leukocytes into the locus. The percentage of macrophages in the total leukocytes was larger in IC-induced otitis media than that in antigen-induced otitis media. These findings suggest that cellular events in the early stage of IC-induced otitis media may be different from antigen-induced otitis media.
CT Check Tags: Comparative Study
Animals
*Chinchilla: IM, immunology
Disease Models, Animal
Exudates and Transudates: CY, cytology
Exudates and Transudates: IM, immunology
Immune Complex Diseases: BL, blood
*Immune Complex Diseases: CO, complications
Immune Complex Diseases: IM, immunology
Leukocyte Count
Macrophages
Neutrophils
Otitis Media with Effusion: BL, blood
***Otitis Media with Effusion: ET, etiology**
Otitis Media with Effusion: IM, immunology
Proteins: AN, analysis
Research Support, U.S. Gov't, P.H.S.
Tympanic Membrane
alpha 1-Antitrypsin: AN, analysis
alpha-Macroglobulins: AN, analysis
CN 0 (Proteins); 0 (**alpha 1-Antitrypsin**); 0 (alpha-Macroglobulins)

L113 ANSWER 12 OF 19 MEDLINE on STN
AN 87323796 MEDLINE
DN PubMed ID: 2443031
TI Kinetics of lysosomal protease activity in human otitis media with effusion.
AU Hamaguchi Y; Sakakura Y; Majima Y; Juhn S K
SO American journal of otolaryngology, **(1987 Jul-Aug)** 8 (4) 194-8.
Journal code: 8000029. ISSN: 0196-0709.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198710
ED Entered STN: 19900305
Last Updated on STN: 20000303
Entered Medline: 19871022

AB Hydrolytic activity of various lysosomal proteases--elastase, collagenase, and cathepsins B and H--were measured in 125 middle ear effusions from patients with chronic (serous and mucoid) and acute otitis media with effusion (OME). The levels of cathepsin B activity and alpha-2-macroglobulin during the course of clinical therapies (myringotomy and tympanostomy tubing) were analyzed in 10 chronic OME cases where follow-up evaluation was possible. It is found that the level of lysosomal protease activity (elastase, collagenase and cathepsin B) was higher in acute OME than that in chronic OME; the hydrolytic activity of cathepsin B in middle ear effusions could be used as an indicator to reflect the level of lysosomal proteases activity in the middle ear; in chronic OME, inflammatory reaction including lysosomal protease activity of the middle ear mucosa at the time of the first myringotomy appeared to be more active than that at the time of the final myringotomy, but less than that in acute OME; and the proteolytic damage of lysosomal thiol proteases to the middle ear mucosa, which may be related to the chronicity of OME, could be reduced by both therapeutic myringotomy and tympanostomy.

CT Check Tags: Female; Male
Cathepsin B: ME, metabolism
Cathepsins: ME, metabolism
Child
*Cysteine Endopeptidases
Follow-Up Studies
Humans
Kinetics
*Lysosomes: EN, enzymology
Microbial Collagenase: ME, metabolism
Middle Ear Ventilation
***Otitis Media with Effusion: EN, enzymology**
Pancreatic Elastase: ME, metabolism
*Peptide Hydrolases: ME, metabolism
alpha-Macroglobulins: ME, metabolism

CN 0 (alpha-Macroglobulins); EC 3.4.- (Cathepsins); EC 3.4.- (Peptide Hydrolases); EC 3.4.21.36 (Pancreatic Elastase); EC 3.4.22 (Cysteine Endopeptidases); EC 3.4.22.1 (Cathepsin B); EC 3.4.22.16 (cathepsin H); EC 3.4.24.3 (Microbial Collagenase)

L113 ANSWER 13 OF 19 MEDLINE on STN
AN **86241753** MEDLINE
DN PubMed ID: **3835890**
TI The significance of protease inhibitors in the pathogenesis of otitis media with effusion.
AU Hamaguchi Y; Majima Y; Ukai K; Sakakura Y; Miyoshi Y
SO Auris, nasus, larynx, **(1985)** 12 Suppl 1 S145-7.
Journal code: 7708170. ISSN: 0385-8146.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198607
ED Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860707

AB Concentration of **alpha 1-antitrypsin** (**alpha 1**-AT), **alpha 1** -antichymotrypsin (**alpha 1**-AChyT), inter-alpha-**trypsin inhibitor** (I-alpha-I), and alpha 2-macroglobulin (alpha 2-M) was measured in 27 serous middle ear effusions (MEEs) from 24 adult patients. The presence of protease-**inhibitor** complex was analyzed by crossed immunoelectrophoresis (CIEP). Mean concentration of

alpha 1-AT was 361 +/- 90.0 mg/dl and was higher than that of other **inhibitors**: **alpha 1**-AChyT, 80.6 +/- 40.7; I-alpha-I, 21.3 +/- 21.5; alpha 2-M, 59.5 +/- 57.1. Molar concentration of alpha 2-M was the lowest. Most of **alpha 1**-AT and **alpha 1**-AChyT in MEEs were unsaturated; free **inhibitors. Alpha-1**-AT could be saturated by **trypsin** and elastase immediately, and only alpha 2-M could be saturated by papain (classical thiol protease). Serous MEEs have high **anti-trypsin** activity attributed to mainly free **alpha 1**-AT. Since level of alpha 2-M was very low, lysosomal thiol proteases could be one of the major proteases inducing proteolytic damage to middle ear mucosa.

CT Adult
Ear, Middle
*Exudates and Transudates: AN, analysis
Humans
Mucous Membrane: ME, metabolism
***Otitis Media with Effusion: ME, metabolism**
*Protease Inhibitors: AN, analysis
CN 0 (Protease Inhibitors)

L113 ANSWER 14 OF 19 MEDLINE on STN
AN **83229348** MEDLINE
DN PubMed ID: **6602580**
TI Middle ear disorders in patients with **alpha 1-antitrypsin** deficiency.
AU Carlsson B
SO Annals of otology, rhinology, and laryngology, **(1983 May-Jun)** 92 (3 Pt 1) 300-4.
Journal code: 0407300. ISSN: 0003-4894.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198307
ED Entered STN: 19900319
Last Updated on STN: 19900319
Entered Medline: 19830715
AB As it is not known whether individuals with **alpha 1-antitrypsin** deficiency show increased sequelae following otitis media, 52 patients with **alpha 1-antitrypsin** deficiency were studied with respect to history of middle ear disease, presence of irreversible pathologic changes of the tympanic membranes, and hearing ability. The middle ear status was determined on otomicroscopy, tympanometry, and pure-tone audiometry. The frequency of individuals with a history of otitis media was 50%. The frequency of individuals with pathologic tympanic membrane changes was no different from that shown in the results obtained in a Swedish normal population study. Minor conductive hearing losses were found in three patients of which only one was related to a history of middle ear disease. However, the history of acute severe complications from otitis media revealed a higher frequency in those individuals with **alpha 1-antitrypsin** deficiency as compared to normals.
CT Check Tags: Female; Male
Adolescent
Adult
Aged
Ear Diseases: ET, etiology
Hearing Disorders: ET, etiology
Hearing Tests

Humans
Middle Aged
***Otitis Media: CO, complications**
Otitis Media: PA, pathology
Phenotype
Risk
Tympanic Membrane: PA, pathology
***alpha 1-Antitrypsin Deficiency**

L113 ANSWER 15 OF 19 MEDLINE on STN
AN 82203720 MEDLINE
DN PubMed ID: 6177249
TI The enzymatic mechanism of the otospongiotic disease and NaF action on the enzymatic balance.
AU Causse J R; Uriel J; Berges J; Shambaugh G E Jr; Bretlau P; Causse J B
SO American journal of otology, **(1982 Apr)** 3 (4) 297-314.
Journal code: 7909513. ISSN: 0192-9763.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198207
ED Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19820719
AB Extensive research on enzymes led to the discovery of the innermost mechanism of the otospongiotic disease. The authors present the results of multiple correlations made from February 1976 to September 1980 on 648 samples of perilymph taken during stapedectomies performed on otosclerotic patients. We studied microdosages of three selected enzymes--**trypsin**, **alpha 1 antitrypsin**, and alpha 2 macroglobulin--in each of the samples and their relationship with cochlear deterioration expressed in dBs of bone conduction decrease in pure-tone audiometry testing. This study allowed us a better knowledge of the enzymatic mechanism of the otospongiotic disease, based on the previously reported **trypsin-alpha 1 antitrypsin** balance, but in which alpha 2 macroglobulin appears to play a role as essential as that of **alpha 1 antitrypsin.** This enzymatic mechanism explains NaF efficiency, which is due in fact to a double action: not only direct **trypsin inhibition**, but also an overall reduction in enzymatic values in the perilymph of otospongiotic/otosclerotic patients. Current studies could lead to the possibility of future NaF replacement by proteinase **inhibitors** either of microbial origin, under study by Japanese researchers, or even of synthetic origin, which should be investigated. In fact, the role of NaF therapy could already be taken over by diphosphonates currently under study.
CT Audiometry, Pure-Tone
Bone Conduction
***Cochlea: PA, pathology**
*Fluorides: TU, therapeutic use
Humans
Labyrinth Diseases: EN, enzymology
***Otosclerosis: EN, enzymology**
Perilymph: EN, enzymology
*Sodium Fluoride: TU, therapeutic use
Stapes Surgery
Trypsin: ME, metabolism
Trypsin Inhibitors: ME, metabolism
alpha-Macroglobulins: ME, metabolism

RN 7681-49-4 (Sodium Fluoride)
CN 0 (Fluorides); 0 (Trypsin Inhibitors); 0 (alpha-Macroglobulins); EC 3.4.21.4 (Trypsin)

L113 ANSWER 16 OF 19 MEDLINE on STN
AN 82133477 MEDLINE
DN PubMed ID: 6174065
TI [Enzymatic mechanism of otosclerosis. Action of NaF].
Mechanisme enzymatique de l'otospongiose. Action du NaF.
AU Causse J R; Uriel J; Berges J; Bretlau P; Causse J B
SO Annales d'oto-laryngologie et de chirurgie cervico faciale : bulletin de la Societe d'oto-laryngologie des hopitaux de Paris, **(1981)** 98 (6) 269-97.
Journal code: 9431026. ISSN: 0003-438X.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA French
FS Priority Journals
EM 198204
ED Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19820420
AB The authors present the conclusions they reached after more than four years of multiple correlations made from february 1976 to september 1980. 648 perilymph samples were selected from a total number of 811 samples taken during stapedectomies on otosclerotic patients. These multiple correlations were based on micro-dosages of three selected enzymes (**trypsin-alpha 1 antitrypsin** and alpha 2 macroglobulin, the fourth cathepsin B having not been found, even in perilymph pools) in each of the selected samples, and on their relationship with the cochlear deterioration expressed in dBs of B.C. decrease and in audiometric stages corrected with reference to the patients' age. This study leads to an enzymatic mechanism, based on the previously reported **trypsin-alpha 1 antitrypsin** balance, but in which alpha 2 macroglobulin appears to play as essential a role as that of **alpha 1** A. This enzymatic mechanism explains NaF efficiency, due in fact to a double action, not only to direct **trypsin inhibition**, but also to an overall reduction in enzymatic levels in the perilymph of otosclerotic patients. The authors conclude by suggesting the possibility of future NaF replacement by proteinase **inhibitors**, either of microbial origin currently under study by Japanese researchers, or even of synthetic origin.
CT Check Tags: Comparative Study
Adult
Aged
Audiometry
English Abstract
*Fluorides: PD, pharmacology
Humans
Middle Aged
Otosclerosis: DT, drug therapy
***Otosclerosis: EN, enzymology**
Perilymph: EN, enzymology
*Sodium Fluoride: PD, pharmacology
Sodium Fluoride: TU, therapeutic use
Stapes Surgery
Trypsin: AN, analysis
Trypsin Inhibitors
alpha 1-Antitrypsin: AN, analysis

alpha-Macroglobulins: AN, analysis
RN 7681-49-4 (Sodium Fluoride)
CN 0 (Fluorides); 0 (Trypsin Inhibitors); 0 (**alpha 1-Antitrypsin**); 0 (alpha-Macroglobulins); EC 3.4.21.4 (Trypsin)

L113 ANSWER 17 OF 19 MEDLINE on STN
AN **77191566** MEDLINE
DN PubMed ID: **140959**
TI [The investigation of a low molecular acid stable proteinase inhibitor in the middle ear secretion (author's transl)].
Der Nachweis eines niedermolekularen saurestabilen Proteinaseninhibitors im Ohrsekret bei chronischer Mittelohreiterung.
AU Kastenbauer E R; Hochstrasser K; Reichert R; Brohr T
SO Laryngologie, Rhinologie, Otologie, **(1977 Mar)** 56 (3) 201-6.
Journal code: 7513628. ISSN: 0340-1588.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 197707
ED Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19770723
AB The proteolytic activity of different proteinases during chronic otitis media can be **inhibited** by alpha-2-macroglobulin and **alpha-1-antitrypsin.** A new low molecular (13,000) acid stable and polyvalent proteinase **inhibitor** could be investigated in the middle ear secretion from patients with cholesteatoma and chronic otitis media. We believe that this **inhibitor** is identical with the low molecular **inhibitor** of bronchial mucus and the nasal fluid. This **inhibitor** shows a high anti proteolytic capacity and can inactive **trypsin**, chymotrypsin, pronase and leucocytic preoteinases. The **inhibitor** is not detectable in any case. We could find it in 55 cases, three specimens of middle ear secretions obtained no acid stable **inhibitor.** It is present in the secretion in a masked form by in situ-reaction with leucocytic proteinases. By denaturating deproteinizing it is liberated out of the complex with proteinases and can be measured. The investigations demonstrate that the level of the **inhibitor** varies during the course of a chronic otitis media. In the postoperative phase the **inhibitor** concentrations were clearly higher than preoperatively. A steep drop of **inhibitor** can be observed in cases of chronic otitis with the symptomatology of an acute inflammation. In cases with a chronic inflammation the **inhibitor** level seems to remain low. The decrease of the **inhibitor** is explained as a using up effect during reaction between **inhibitor** and leucocytic proteinases. We believe that this **inhibitor** in the middle ear secretion results from a limited proteolysis and splitting of inter-alpha-**trypsin inhibitor** by a proteolytic enzyme, possibly by kallikrein.
CT **Ear, Middle: EN, enzymology**
***Ear, Middle: SE, secretion**
English Abstract
Humans
Molecular Weight
***Otitis Media: EN, enzymology**
Otitis Media: PP, physiopathology
*Protease Inhibitors
CN 0 (Protease Inhibitors)

L113 ANSWER 18 OF 19 MEDLINE on STN
AN **77055330** MEDLINE
DN PubMed ID: **63098**
TI [The effect of ear surgery to the immunologic defense system of the middle ear during chronic otitis media (author's transl)].
Der Operationseffekt auf das immunologische Abwehrsystem des Mittelohres bei der chronischen Ohreiterung.
AU Kastenbauer E R; Hochstrasser K; Brohr T
SO Laryngologie, Rhinologie, Otologie, **(1976 Oct)** 55 (10) 804-12.
Journal code: 7513628. ISSN: 0340-1588.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 197701
ED Entered STN: 19900313
Last Updated on STN: 19900313
Entered Medline: 19770125
AB **Alpha-1-antitrypsin** and alpha-2-macroglobuline are very important proteinase inhibitors for the healing process in chronic otitis media, because they can inhibit numerous bacterial and leukocytic proteinases: Alpha-2-macroglobuline can block the malignant proteinases of pseudomonas aeruginosa, staphylococcus aureus and proteus vulgaris. In 58 cases in the middle ear secretion was examined and the level of **alpha-1-antitrypsin** and alpha-2-macroglobulin investigated pre- and postoperatively. By these investigations we could demonstrate that the postoperative level of these two inhibitors is higher than preoperatively. In a couple of cases with cholesteatoma the postoperative concentration of alpha-2-macroglobuline was nearly three times higher than prior to the tympanoplasty. We believe that one of the causes for this high inhibitor level is the liberation of alpha-2-macroglobuline by injuring blood vessels during a tympanoplasty. It is our opinion that the increase of the inhibitor level in the postoperative phase is one of the prerequisites for the healing process in chronic otitis media.
CT Antibody Formation
Chronic Disease
***Ear, Middle: IM, immunology**
English Abstract
Humans
Immunoglobulins
***Otitis Media: SU, surgery**
Postoperative Complications: BL, blood
Postoperative Complications: IM, immunology
alpha 1-Antitrypsin: ME, metabolism
alpha-Macroglobulins: ME, metabolism
CN 0 (Immunoglobulins); 0 (**alpha 1-Antitrypsin**); 0 (alpha-Macroglobulins)

L113 ANSWER 19 OF 19 MEDLINE on STN
AN 74043966 MEDLINE
DN PubMed ID: 4758137
TI Management of general anesthesia for mastoid-tympanoplasty: anesthesia and surgical considerations.
AU Snow J C; Kripke B J; Strong M S
SO Laryngoscope, **(1973 Nov)** 83 (11) 1786-93.
Journal code: 8607378. ISSN: 0023-852X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 197401
ED Entered STN: 19900310
Last Updated on STN: 19990129
Entered Medline: 19740130
CT Adolescent
Adult
Aged
Alanine Transaminase: BL, blood
*Anesthesia, Inhalation
Bicarbonates: BL, blood
Carbon Dioxide: BL, blood
Child
Electrocardiography
*Halothane
Halothane: AE, adverse effects
Humans
Hydrogen-Ion Concentration
*Hypotension, Controlled
Isoenzymes
L-Lactate Dehydrogenase: BL, blood
Leucyl Aminopeptidase: BL, blood
Liver: DE, drug effects
Liver Function Tests
*Mastoid: SU, surgery
Middle Aged
Oxygen: BL, blood
Trimethaphan: DU, diagnostic use
***Tympanoplasty**
RN 124-38-9 (Carbon Dioxide); 151-67-7 (Halothane); 7187-66-8 (Trimethaphan); 7782-44-7 (Oxygen)
CN 0 (Bicarbonates); 0 (Isoenzymes); EC 1.1.1.27 (L-Lactate Dehydrogenase); EC 2.6.1.2 (Alanine Transaminase); EC 3.4.11.1 (Leucyl Aminopeptidase)

=> => fil wpix
FILE 'WPIX' ENTERED AT 15:48:50 ON 21 JUN 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

FILE LAST UPDATED: 16 JUN 2005 <20050616/UP>
MOST RECENT DERWENT UPDATE: 200538 <200538/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE http://thomsonderwent.com/coverage/latestupdates/ <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://thomsonderwent.com/support/userguides/ <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX FIRST VIEW - FILE WPIFV.
FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.

PLEASE CHECK:
http://thomsonderwent.com/support/dwpiref/reftools/classification/code-revision/
FOR DETAILS. <<<

=> d all abeq tech abex tot

L151 ANSWER 1 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2005-182067 [19] WPIX
DNC C2005-058121
TI New peptide compounds useful in the treatment of e.g. central and peripheral nervous system disorders, muscles disorders, diseases of various organs such as gonads and pancreas, cancer, and prion diseases.
DC B04 D16
IN ALBRECHTSEN, M; BEREZIN, V; BOCK, E; HOLM, A
PA (ENKA-N) ENKAM PHARM AS
CYC 108
PI WO 2005014623 A2 20050217 (200519)* EN 195 C07K007-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2005014623 A2 WO 2004-DK527 20040806
PRAI DK 2004-814 20040525; DK 2003-1141 20030807
IC ICM C07K007-00
AB WO2005014623 A UPAB: 20050321
NOVELTY - Peptide compounds comprising two individual peptide sequences, are new.

DETAILED DESCRIPTION - Peptide compounds comprising two individual peptide sequences. At least one of the peptide sequences is a sequence of formula L1-A-L2-B-L3-C-L4-D-L5 (I). The peptide sequences are connected to each other through linker of formula X((A1)nCOOH)((B1)mCOOH) (II).

A - D = hydrophobic amino acid residue, basic amino acid residue, Asn, Gln, acidic amino acid residue, Asn, Gln, Gly or Ala;

L1 - L5 = chemical bond or an amino acid sequence having n1 amino acid residues;

n1 = 0 - 5;

n, m and p = 1 - 20;

X = HN, H2N(CR2)pCR, RHN(CR2)pCR, HO(CR2)pCR, HS(CR2)pCR, halogen(CR2)pCR, HOOC(CR2)pCR, ROOC(CR2)pCR, HCO(CR2)pCR, RCO(CR2)pCR, (HOOC(A1)n)(HOOC(B1)m)CR(CR2)pCR, H2N (CR2)p, RHN(CR2)p, HO(CR2)p, HS(CR2)p, halogen(CR2)p, HOOC(CR2)p, ROOC(CR2)p, HCO(CR2)p, RCO(CR2)p, or (HOOC(A1)n)(HOOC(B1)m)(CR2)p;

R and R2 = not defined;

A1 and B1 = 1-10C alkyl, 2-10C alkenyl, cyclic moiety, heterocyclic moiety or aromatic moiety (all optionally substituted);

A1+B1 = cyclic, heterocyclic, or aromatic moiety.

An INDEPENDENT CLAIM is included for preparation of the peptide compounds by ligand presenting assembly method.

ACTIVITY - CNS-Gen.; Cerebroprotective; Antiparkinsonian; Neuroprotective; Nootropic; Anticonvulsant; Antidiabetic; Antimanic; Antidepressant; Neuroleptic; Muscular-Gen.; Nephrotropic; Cardiant; Hepatotropic; Gastrointestinal-Gen.; Cytostatic; Vulnerary; Vasotropic; Antialcoholic; Ophthalmological; Auditory; Respiratory-Gen.; Antiarrhythmic.

The Neuroprotective efficacy of a peptide compound of formula T1-CO-CH2-NH-CH2-CO-T1 (FGL-L) (where T1 is -Glu-Val-Tyr-Val-Val-Ala-Glu-Asn-Gln-Gln-Gly-Lys-Ser-Lys-Ala-NH2) (IIa) was evaluated by analyzing

behavior and memory of rats in which cognitive impairment was induced by beta -amyloid fragment. (IIa) Was administered sub-occipitally at days 7, 10, and 13 following intracerebroventricular administration of the beta -amyloid fragment. Administration of beta -amyloid fragment caused significant increase in the time spent by the rat exploring a juvenile animal at a second meeting as well as amyloid burden and neuronal cell death. However treatment with (IIa) significantly reduced significant increase in the time spent by the rat exploring a juvenile animal at a second meeting. In rats treated/untreated with (IIa), the amyloid burden (%) in cingulated cortex was found to be 39/100; and density of neurons (neurons/mcm2 multiply 10-4) in hippocampus zone was found to be 22/15. (IIa) Was found to prevent short-term memory deficit and ameliorate neuropathological changes in the brain tissue.

MECHANISM OF ACTION - Fibroblast growth factor receptor (FGFR) modulator.

USE - In the manufacture of medicament for the treatment of conditions of the central and peripheral nervous system associated with postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias (e.g. multiinfarct dementia), sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, schizophrenia, and mood disorders such as manic depression; diseases or conditions of the muscles including conditions with impaired function of neuro-muscular connections, such as after organ transplantation, and genetic or traumatic atrophic muscle disorders; diseases or conditions of various organs, such as degenerative conditions of the gonads, of the pancreas such as diabetes mellitus Type I and II, of the kidney such as nephrosis and of the heart, liver and bowel; also for the treatment of cancer (e.g. solid tumors requiring neoangiogenesis); for the promotion of wound-healing; for the prevention of death of heart muscle cells, such as after acute myocardial infarction, or after angiogenesis; for revascularisation; for the stimulation of the ability to learn and the short as well as long-term memory; for the prevention of cell death due to ischemia, and body damages due to alcohol consumption; for the treatment of prion diseases (all claimed). Also for the treatment of epilepsy, amyotrophic lateral sclerosis, disorders affecting multiple structures of eyes and **ears**, arrhythmia and diseases in pulmonary system.

ADVANTAGE - The compounds are capable of low affinity binding to fibroblast growth factor receptor (FGFR); exhibit excellent FGFR modulatory activity; and thus are important in treatment and prevention of different pathological conditions.

Dwg.0/28

FS CPI

FA AB; DCN

MC CPI: B04-C01; B04-C01H; B14-E10C; B14-F01A; B14-F01B; B14-F02; B14-G02C; B14-H01; B14-J01; B14-J05; B14-J07; B14-K01; B14-M01A; **B14-N02**; B14-N03; B14-N07; B14-N10; B14-N12; B14-N13; B14-N16; B14-N17B; B14-S04; D05-H17A

TECH UPTX: 20050321

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation (claimed): Preparation of the peptide compounds by ligand presenting assembly method involves:
(1) providing ligands comprising desired sequence(s) by solid phase synthesis or fragment coupling, where the ligands are attached to a solid phase;
(2) optionally deprotecting N-terminal amino acid groups while the ligands are still attached to the solid phase;
(3) reacting the ligand(s) having unprotected N-terminal groups with an achiral di-, tri- or tetracarboxylic acid so as to provide a construct

having a ring structure; and
(4) cleaving the construct from the solid phase so as to provide an LPA comprising ligands having free C-terminal groups.
TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: At least one of the peptide sequences is capable of binding to a functional cell surface receptor. The functional cell surface receptor is a receptor selected from the family of fibroblast growth factor receptors (FGFRs) (e.g. FGFR1, FGFR2, FGFR3, FGFR4, or their functional homologues).
The peptide sequence is derived from the sequence of a polypeptide selected from cell adhesion molecule, cell-surface receptor, heparan sulfate proteoglycans, **metalloprotease**, extracellular **matrix** molecule and growth factor (preferably the peptide sequence is selected from 146 sequences as given in the specification, e.g. Glu-Val-Tyr-Val-Val-Ala-Glu-Asn-Gln-Gln-Gly-Lys-Ser-Lys-Ala, Asn-Ile-Glu-Val-Trp-Val-Glu-Ala-Glu-Asn-Ala-Leu-Gly-Lys-Lys-Val, their fragments, variants or homologues).
The cell adhesion molecule is selected from 24 molecules, their fragments and variants as given in the specification, e.g. Neural Cell Adhesion Molecule (NCAM) (Swiss-Prot Ass. Nos: P13591, P13595-01, P13595), Axonin-1/TAG-1 (Swiss-Prot Ass. Nos: Q02246, P22063, P28685), and Cadherin (Swiss-Prot Ass. No: Q9VW71). The cell-surface receptor is selected from 30 receptors as given in the specification, e.g. Fibroblast Growth Factor Receptor 1 (FGFR1) (Swiss-Prot Ass. Nos: Q9QZM7, Q99AVV7, Q9UD50, Q63827), Fibroblast Growth Factor Receptor 2 (FGFR2) (Swiss-Prot Ass. Nos: Q96KM2, P21802, Q63241), Leukocyte Antigen Related Protein-Tyrosine Phosphatase (LAR-PTPRF) (Swiss-Prot Ass. Nos: Q9EQ17, Q64605, Q64604, Q9QW67, Q9VIS8, P10586), Insulin Receptor (IR) (Swiss-Prot Ass. No: Q9PWN6), and Interleukin-6 Receptor (IL-6R) (Swiss-Prot Ass. No: Q00560). The heparan sulfate proteoglycan is periecan (Swiss-Prot Ass. No: P98160), its fragment or variant. The **metalloprotease** is selected from 12 **metalloproteases** as given in the specification, e.g. ADAM-8 (Swiss-Prot Ass. No: Q05910), ADAM-19 (Swiss-Prot Ass. No: Q9H013, 035674). The extracellular **matrix** molecule is collagen type VII (Swiss-Prot Ass. No: Q63870), Fibronectin (Swiss-Prot Ass. Nos: Q95KV4, Q95KV5, P07589, Q28377, U42594, 095609, P11276), or Tenascin-R (Swiss-Prot Ass. Nos: Q15568, O00531, Q90995, P10039), their fragments or variants.
The growth factor is cytokine-like factor-1 (CLF-1) (Swiss-Prot Ass. No: 075462), its fragment or variant.

ABEX UPTX: 20050321

ADMINISTRATION - Dosage (mug/kg) of the peptide compounds is 0.1 - 5000 (preferably 0.1 - 1000) or 0.1 - 1000 (preferably 0.1 - 250) when administered in monomeric or multimeric forms respectively. Administration is by oral, percutaneous, intramuscular, intravenous, intracranial, intrathecal, intracerebroventricular; intranasal, rectal, nasal, or pulmonary route.

EXAMPLE - A peptide compound of formula T1-CO-CH2-NH-CH2-CO-T1 (FGL-L) (where T1 is -Glu-Val-Tyr-Val-Val-Ala-Glu-Asn-Gln-Gln-Gly-Lys-Ser-Lys-Ala-NH2) was made by coupling N-tert-butyl oxycarbonyl-iminodiacetic acid to the peptide on the resin using O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate/1-hydroxybenzotriazol as described in WO 00/18791. The peptide was cleaved from the resin and simultaneously deprotected on the side chains on TFA in the presence of TES and water. The resultant LPA-type dimmer (0.5 mg/ml) was purified by reverse phase HPLC.

L151 ANSWER 2 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2005-132500 [14] WPIX
DNC C2005-043705
TI New tetracycline compounds useful to treat e.g. bacterial, viral and

parasitic infections, cancer, bone mass disorders and neurological disorders.

DC B03 B05

IN AMOO, V; ASSEFA, H; BERNIAC, J; BHATIA, B; BOWSER, T; CHEN, J; GRIER, M; HONEYMAN, L; KIM, O; MECHICHE, R; OHEMENG, K; PAN, J

PA (PARA-N) PARATEK PHARM INC

CYC 108

PI WO 2005009944 A1 20050203 (200514)* EN 45 C07C237-26
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

ADT WO 2005009944 A1 WO 2004-US20305 20040625

PRAI US 2004-566150P 20040427; US 2003-486017P 20030709;
US 2003-525287P 20031125; US 2003-530123P 20031216

IC ICM C07C237-26
ICS A61K031-65

AB WO2005009944 A UPAB: 20050228
NOVELTY - Tetracycline compounds (A) and their salts are new.
DETAILED DESCRIPTION - Tetracycline compounds (A) of formulae (I)-(IV) and their salts are new.
E = O, N or a covalent bond;
G = alkyl, heterocyclicalkyl, aryl, alkylcarbonyloxyalkyl, arylcarbonyloxyalkyl or alkoxyalkoxycarbonyloxyalkyl;
Q1 = a prodrug moiety and its salts (preferably (C=O)-E1-G1);
E1 = O, N or a covalent bond (preferably O);
G1 = alkyl, heterocyclicalkyl, aryl, alkylcarbonyloxyalkyl, arylcarbonyloxyalkyl, alkyloxycarbonyloxyalkyl, arylalkylcarbonyloxyalkyl, alkyloxyalkylcarbonyloxyalkyl or alkoxyalkoxycarbonyloxyalkyl (especially alkylcarbonyloxyalkyl, most preferably (CH2)m-O-(C=O)-R7);
m = 1-5 (preferably 1);
R7 = alkyl (preferably methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, (CH2)10-CH3 or (CH2)11-CH3);
Q2 = a prodrug moiety or its salt (preferably (C=O)-G2);
G2 = alkyloxycarbonylalkyl or alkyl;
Q3 = a prodrug moiety or its salt (preferably (C=O)-E3-G3);
E3 = O, N or a covalent bond (preferably O); and
G3 = alkyl, heterocyclicalkyl, aryl, alkylcarbonyloxyalkyl, arylcarbonyloxyalkyl, alkyloxycarbonyloxyalkyl, arylalkylcarbonyloxyalkyl, alkyloxyalkylcarbonyloxyalkyl or alkoxyalkoxycarbonyloxyalkyl (preferably aryl or alkyl (both optionally substituted)).
ACTIVITY - Antibacterial; Virucide; Antiparasitic; Fungicide; Cytostatic; Antiarthritic; Osteopathic; CNS-Gen.; Respiratory-Gen.; Antidiarrheic; Uropathic; Dermatological; Auditory; Vulnerary; Antiinflammatory; Antimalarial; Vasotropic; Cerebroprotective; Ophthalmological; Antiulcer; Antidiabetic; Neuroprotective; Nootropic.
An assay to determine the efficacy of tetracycline compounds (A) against common bacteria is described, but no results are given.
MECHANISM OF ACTION - None given.
USE - (A) are useful to treat tetracycline responsive states (bacterial infections, viral infections or parasitic infections; where the bacterial infection (gram positive or gram negative) is associated with E. coli, S. aureus or E.faecalis; and the infection is resistant to other tetracycline antibiotics) in subjects (preferably humans) (claimed). (A) are useful to treat fungal infections, cancer (e.g. prostate cancer and melanoma), neoplasms, arthritis, osteoporosis, cystic fibrosis, diarrhea, urinary tract infections, infections of skin and skin structure,

ear, nose and throat infections, wound infection, mastitis, inflammatory process associated states (e.g. osteoarthritis and upper respiratory infections), nitric oxide associated states (e.g. malaria and vascular stroke), **matrix metalloproteinase** associated states (e.g. corneal ulceration and emphysema), acute lung injury, diabetes (e.g. juvenile diabetes), bone mass disorders (e.g. osteoporosis and Paget's disease), chronic lung disorders, ischemia, stroke, ischemic stroke, skin wound, neurological disorders (e.g. Alzheimer's disease and dementias), aortic or vascular aneurysm in vascular tissue and other states for which (A) have been found to be active.

ADVANTAGE - (A) is substantially non-toxic when compared to other cancer treatments.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B02-T; B14-A01; B14-A01A; B14-A01A3; B14-A01B; B14-A01B4; B14-A02; B14-A03B; B14-A04; B14-B02; B14-C03; B14-C09; B14-C09A; B14-D07C1; B14-E02; B14-E08; B14-F01; B14-F02; B14-F02D; B14-F02D1; B14-H01; B14-H01B; B14-J01; B14-J01A4; B14-K01; B14-N01; B14-N01A; **B14-N02**; B14-N04; B14-N05B; B14-N07; B14-N16; B14-N17; B14-N17B; B14-N18; B14-S04; B14-S16

TECH UPTX: 20050228

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Disclosed preparation of (I) comprises:

(a) reaction of a tetracycline compound of formula (a) with N-hydroxy benzopyrole-2,7-dione in the presence of methylamine, methanol and hydrochloric acid; and

(b) reaction of the obtained amino tetracycline compound of formula (b) with 3,3-dimethyl-butyraldehyde in the presence of sodiumhypoboroacetate and dimethylformamide to give a tetracycline compound of formula (c) (representative compound of (I)).

Preferred Method: For the treatment of diseases, (A) is administered with a pharmaceutically acceptable carrier; and (A) is metabolized in vivo to tetracycline compounds of formulae (1)-(4).

ABEX UPTX: 20050228

SPECIFIC COMPOUNDS - 33 compounds (A) are specifically claimed e.g. N-t-butylcarbonyloxymethyl (9-((2,2-dimethyl-propylamino)-methyl)-minocycline) carbamate of formula (Ia).

ADMINISTRATION - Administration of (A) is 0.01-100 (preferably 1-20) mg/kg/day, orally, parenterally or topically.

EXAMPLE - A mixture of sodium bicarbonate (3.21 g), tetrabutylammonium sulfate (6.49 g), pentanoic acid (1.95 g), water (38.5 ml) and dichloromethane (38.5 ml) was stirred for 1 hour. A solution of crude thiocarbonic acid O-iodomethyl ester S-ethyl ester (3.5 g) in dichloromethane (7 ml) was added over a 0.5 hour period and the temperature was maintained below 30degreesC. The mixture was then stirred for further 1.5 hours at room temperature. The reaction mixture was worked up to give 2,2-dimethyl propionic acid ethylsulfanylcarbonyl oxymethyl ester (i). Sulfuryl chloride (0.68 ml) was added to (i) (1.84 g) at 0-5degreesC with stirring over 5 minutes. The solution was worked up to give t-butylcarbonyloxymethyl chloroformate (ii). To a mixture of 9-((2,2-dimethyl-propyl amino)-methyl)-minocycline (0.1 g), sodium bicarbonate (63 mg) in water (1 ml) and dichloromethane (20 ml) was added the t-butylcarbonyloxymethyl chloroformate (44 mg). The reaction mixture was worked up to give N-t-butylcarbonyloxymethyl (9-((2,2-dimethyl-propylamino)-methyl)-minocycline) carbamate (25 mg).

DEFINITIONS - Preferred Definitions: In (I),

E = either a covalent bond (where G is alkyl); or a nitrogen (where G is aryl; preferably substituted phenyl); or an oxygen (where G is alkylcarbonyloxyalkyl (preferably (CH2)g-O-(C=O)-R1), alkyloxycarbonyloxyalkyl (preferably (CH2)-O-(C=O)-O-R3), arylcarbonyloxyalkyl (preferably (CH2)f-O-(C=O)-R2), alkyl (preferably methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, (CH2)10-CH3 or (CH2)11-CH3), alkyloxycarbonyloxyalkyl (preferably (CH2)-O-(C=O)-O-R3), arylalkylcarbonyloxyalkyl (preferably (CH2)-O-(C=O)-(CH2)h-R4), alkyloxyalkylcarbonyloxyalkyl (preferably (CH2)-O-(C=O)-(CH2)i-R5), alkoxyalkoxyalkylcarbonyloxyalkyl (preferably (CH2)-O-(C=O)-(CH2)j-O-(CH2)k-O-R6));
g = 1-5 (preferably 1, where R1 is alkyl (preferably methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, (CH2)10-CH3, (CH2)11-CH3 or cycloalkyl); or 2 (where R1 is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, (CH2)10-CH3 or (CH2)11-CH3));
f = 1-5 (preferably 1);
R2 = aryl (preferably phenyl optionally substituted with halo, alkoxy and/or alkyl);
R3 = alkyl (preferably methyl, ethyl, propyl, butyl or pentyl);
h = 1-5 (preferably 1-2);
R4 = aryl (preferably phenyl);
i = 1-5 (preferably 1-3);
R5 = methyl;
j and k = 1-5; and
R6 = alkyl (preferably methyl; where j is 1 and k is 2).

L151 ANSWER 3 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-794473 [78] WPIX
CR 2004-783852 [77]; 2004-794491 [78]
DNC C2004-277232
TI Sparing tissue levels of **alpha-1-antitrypsin** in animal for treatment of inflammatory diseases or disorders, or hypotension, comprises administering nitric oxide synthase inhibitor.
DC B05
IN SHAPIRO, L
PA (SHAP-I) SHAPIRO L
CYC 1
PI US 2004220113 A1 20041104 (200478)* 22 A61K038-04
ADT US 2004220113 A1 Div ex US 2003-427929 20030502, US 2003-669250 20030925
PRAI US 2003-427929 20030502; US 2003-669250 20030925
IC ICM A61K038-04
ICS A61K031-4245
AB US2004220113 A UPAB: 20041206
NOVELTY - Sparing tissue levels of **alpha 1-antitrypsin** in animal, comprises administering nitric oxide synthase inhibitor.
ACTIVITY - Vasotropic; Hypertensive; Respiratory-Gen.; Anti-HIV; Neuroprotective; Nootropic; Antiasthamatic; Antiarteriosclerotic; Immunosuppressive; Cardiant; Cytostatic; Antiinflammatory; Cerebroprotective; Cardiovascular-Gen.; Antidiabetic; Analgesic; Gynecological; Antibacterial; Nephrotropic; Ophthalmological; Gastrointestinal-Gen.; Hypotensive; Antiulcer; Hepatotropic; Antimigraine; Antiarthritic; Osteopathic; Antiparkinsonian; Protozoacide; Antianemic; Antisickling; Antirheumatic; Dermatological.
MECHANISM OF ACTION - Serine protease inhibitor; Antagonist.
USE - For sparing tissue levels of **alpha 1-antitrypsin** in animal, e.g. human, and for treatment of inflammatory diseases or disorders, or hypotension, acquired tubulointerstitial disease, acute pancreatitis, acute respiratory failure,

acute respiratory distress syndrome (ARDS), age-associated memory impairment, AIDS, airway inflammation, Alzheimer's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular disease, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic **otitis** media, congestive heart failure, coronary artery disease, coronary artery ectasia, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end-stage renal disease falciparum malaria, gastric carcinogenesis, gastrointestinal pathophysiology, glaucoma, glutamate-induced asthma, glutamate induced Chinese restaurant syndrome, heart failure, heat stress, gastritis, 'hotdog headache', Hirschprung's disease, HIV infection, hypertension, hypoxemic respiratory failure, inflammatory arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), inflammatory joint disease, liver cirrhosis, liver disease, Lyme neuroborreliosis, migraine, multiple sclerosis, neonatal and pediatric respiratory failure, nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, Parkinson's disease, pediatric pulmonary disease, pleural inflammation, preeclampsia, primary ciliary dyskinesia, primary pulmonary hypertension, protozoan infections, pugilistic Alzheimer's disease, pulmonary hypertension, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression, or vascular disease.

ADVANTAGE - The method provides for treatment of diseases dependent on the action of NO and proteases. The serine protease inhibitors exhibit high activity at low concentrations.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B02-T; B04-B04D2; B06-D05; B06-F03; B07-D03; B07-D12; B07-D13; B10-A03; B10-A05; B10-A13A; B10-A17; B10-B01B; B14-A02B1; B14-A03; B14-A03B; B14-C01; B14-C03; B14-C04; B14-C09; B14-D01C; B14-D07C; B14-E10; B14-F01B; B14-F01E; B14-F02; B14-F03; B14-F07; B14-F08; B14-G01B; B14-G02D; B14-H01; B14-J01; B14-K01; B14-L06; B14-N01; B14-N03; B14-N10; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17; B14-S01; B14-S04; B14-S06; B14-S08

TECH UPTX: 20041206

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: The nitric oxide (NO) synthase inhibitor comprises N-G-nitro-L-arginine methyl ester, N-G-nitro-L-arginine N,N'-dimethylarginine, N-G-monoethyl-L-arginine acetate, N-G-monomethyl-L-arginine acetate, N-G-monomethyl-D-arginine, N-G-monomethyl-L-homoarginine acetate, N-G-nitro-D-arginine, N-G-nitro-D-arginine methyl ester gydrochloride, omega-nitro-arginine, L-N6-(1-iminoethyl)lysine, aminoguanidine, S-methylisothiourea sulfate, S-ethylisothiourea sulfate, S-aminoethylisothiourea sulfate, mercaptoethylguanidine, 2,4-diamino-6-hydroxypyrimidine, diphenyleneiudonium chloride, 2-ethyl-2-thiopseudourea hydrobromide, 2-iminobiotin, L-N-5-(1-iminoethyl)ornithine hydrochloride, S-methyl-L-thiocitrulline dihydrochloride, p-nitroblue tetrazolium chloride, 3-bromo-7-nitroindazole, pentamidine isethionate, 1-pyrrolidinecarbodithioic acid, spermidine, spermine, spermine-NO, 3-morpholinosydonimine-N-ethyl-carbamide, L-thiocitrulline, troleandomycin, 7-nitroindazole, hemoglobin, myoglobin, cytochrome V, A-nitroso-N-acetylpenicillamine S-nitrosoglutathione, or nitroglycerine, or their free bases or salts.

ABEX UPTX: 20041206

ADMINISTRATION - Doses are administered at 0.01-20 mg/ml biologic fluid of treated patient, by injection, continuous intravenous infusion, transdermally, or orally.

L151 ANSWER 4 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-783852 [77] WPIX
CR 2004-794473 [78]; 2004-794491 [78]
DNC C2004-274208
TI Use of **alpha-1-antitrypsin**, **alpha-1-antitrypsin**-like agent, antielastase, antiproteinase-3 agent and/or serine protease inhibitor for the treatment of ischemia reperfusion injury.
DC B05
IN SHAPIRO, L
PA (SHAP-I) SHAPIRO L
CYC 1
PI US 2004220239 A1 20041104 (200477)* 22 A61K031-433
ADT US 2004220239 A1 Div ex US 2003-427929 20030502, US 2003-669251 20030925
PRAI US 2003-427929 20030502; US 2003-669251 20030925
IC ICM A61K031-433
ICS A61K031-4245
AB US2004220239 A UPAB: 20041206
NOVELTY - Treatment of ischemia reperfusion injury involves administration of at least one of **alpha 1-antitrypsin**, **alpha 1-antitrypsin**-like agent, antielastase, antiproteinase-3 agent and/or serine protease inhibitor.

ACTIVITY - Vasotropic; Cerebroprotective; Nephrotropic; Nootropic; Neuroprotective; Respiratory-Gen.; Antiinflammatory; Hepatotropic; Anti-HIV; Virucide; Immunosuppressive; Antidiabetic; Auditory; Cardiant; Gynecological; Analgesic; Antibacterial; Ophthalmological; Antimalarial; Gastrointestinal-Gen.; Osteopathic; Antiasthmatic; Antiarteriosclerotic; Protozoacide; Dermatological; Cytostatic; Hypotensive; Antiulcer; Antimigraine; Antianemic; Antisickling; Antirheumatic; Tranquilizer; Vulnerary; Antiarthritic; Antiparkinsonian.

MECHANISM OF ACTION - Nitric oxide synthesis inhibitor. The efficacy of **alpha 1-antitrypsin** (Ia) to inhibit nitric oxide synthesis was evaluated in macrophages. RAW 264.5 cell monolayers of macrophages were treated with (Ia) (0.1 - 3 mg/ml), followed by costimulation with interferon- gamma (10 U/ml) and lipopolysaccharide (1 ng/ml) for 18 hours. After incubation aliquots of supernatant were combined with Greiss reagent and incubated at room temperature for 10 minutes and then nitric oxide concentration was measured colorimetrically. The cell layers were treated with costimulants without (Ia) as control. The produced nitric oxide (nmol of NO2/106 cells) was found to be 1, 2, 4.5 and 8 in the cell supernatant treated with 3, 1 and 0.1 mg/ml of (Ia) and control respectively.

USE - For the treatment of ischemia reperfusion injury associated with heart, brain, lung, kidneys or liver (claimed). Also for the treatment of acute pancreatitis, acute respiratory failure, acute respiratory distress syndrome (ARDS), age-associated memory impairment, AIDS, cytomegalovirus infection, Herpes simplex infection, airway inflammation, Alzheimer's disease, amyotrophic lateral sclerosis, asthma, atherosclerosis, autoimmune disease, myocarditis, carcinogenesis, cerebral ischemia, cerebrovascular disease, chronic liver disease, chronic lung disease, chronic obstructive pulmonary disease, chronic **otitis** media, congestive heart failure, coronary artery disease, diabetes mellitus, diabetic neuropathy, dysfunctional uterine bleeding, dysmenorrhea, endotoxic shock, end-stage renal disease, falciparum malaria, gastrointestinal pathophysiology, glaucoma, glutamate-induced asthma, heart failure, heat stress, gastritis, hypertension, inflammatory arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), inflammatory joint diseases, liver cirrhosis, liver disease, migraine, multiple sclerosis, neonatal and pediatric respiratory failure,

nephrotoxicity, neurodegenerative diseases, orthopedic disease, osteoarthritis, oxidant stress, Parkinson's disease, pediatric pulmonary disease, preeclampsia, primary ciliary dyskinesia, protozoan infections, pulmonary hypertension, retinal disease, septic shock, sickle cell anemia, rheumatoid arthritis, stroke, systemic lupus erythematosus, traumatic brain injury, tumor progression, and vascular disease.

ADVANTAGE - The method is safe and effective for amelioration of many diseases related to nitric oxide-caused damage. The therapeutic agents used exhibit significant potential as nitric oxide synthesis inhibitor, and high activity at relatively low concentration.

Dwg.0/7

FS CPI

FA AB; DCN

MC CPI: B04-C01A; B04-M01; B04-N02; B04-N04A; B07-D03; B07-E04; B14-A02A3; B14-A03; B14-C01; B14-C03; B14-C04; B14-C09; B14-D01C; B14-D07C; B14-E08; B14-E10; B14-F01B; B14-F01E; B14-F02; B14-F03; B14-F05; B14-F07; B14-F08; B14-G01B; B14-G02D; B14-H01; B14-J01; B14-K01; **B14-N02**; B14-N03; B14-N10; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17; B14-S01; B14-S04; B14-S06; B14-S08

TECH UPTX: 20041203

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method further involves administration of a thrombolytic agent; and using a mechanical device to reestablish blood flow. The mechanical device involves angioplasty or percutaneous transluminal coronary angioplasty. Preferred Component: The alpha1-antitrypsin-like agent is a form of alpha1-antitrypsin resistant to inactivation by reactive oxygen intermediates.

ABEX UPTX: 20041203

ADMINISTRATION - Dosage of the compounds is 0.01 - 20 mg/ml of biological fluid of treated patient. Administration is by oral, topical, transdermal, parenteral (including subcutaneous, intravenous, intraarterial, intranasal, intraperitoneal, intramuscular), transbronchial, transalveolar, or rectal route.

EXAMPLE - No relevant example given.

L151 ANSWER 5 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2004-765487 [75] WPIX

CR 2003-342643 [32]; 2004-329624 [30]

DNN N2004-603924 DNC C2004-268299

TI New triazine compounds are smooth muscle proliferation inhibitor useful for treating inflammation mediated disease and hyperproliferative disease.

DC B03 B04 D22 S05 T01

IN ALEXANDER, C W; KRISHNA, R V V; KUMAR, P R; PAL, M; PILLARISETTI, S; REDDY, G O; REDDY, J T; SAXENA, U; SRIDEVI, B S; TIMMER, R T; YELESWARAPU, K R

PA (ALEX-I) ALEXANDER C W; (KRIS-I) KRISHNA R V V R M; (KUMA-I) KUMAR P R; (PALM-I) PAL M; (PILL-I) PILLARISETTI S; (REDD-I) REDDY G O; (REDD-I) REDDY J T; (SAXE-I) SAXENA U; (SRID-I) SRIDEVI B S; (TIMM-I) TIMMER R T; (YELE-I) YELESWARAPU K R

CYC 1

PI US 2004209881 A1 20041021 (200475)* 254 A61K031-53

ADT US 2004209881 A1 US 2003-400134 20030326

PRAI US 2003-400134 20030326

IC ICM A61K031-53
ICS C07D251-48; C07D403-02

AB US2004209881 A UPAB: 20050603

NOVELTY - Triazine compounds (I) are new.

DETAILED DESCRIPTION - Triazine compounds of formula (I) are new. R1b = e.g. 4-fluoro-5-methoxy-pyridin-2-yl, 3-fluoro-2-methoxy-

pyridin-5-yl, 3-fluoro-4-(Na+ O-)-phenyl, 3-fluoro-4-(K+ O-)-phenyl, 3-(trifluoromethyl)-4-methoxyphenyll or 4-methoxy-3-carboxy-phenyl (or its sodium salt);

R2b = e.g. hexahydro-pyrrolo(1,2-c)imidazol-2-yl, hexahydro-pyrrolo(1,2-c)imidazol-3-on-2-yl, 2,3-dihydro-1H-indol-1-yl or 1H-indol-1-yl;

R4b = H, CH3, CH2CH3 or CH2CH2CH3;

R5b = e.g. cycloheptane, cyclohepten-4-yl, azepan-4-yl or 1-methyl-azepan-4-yl;

R6b = O, NH, NCH3, NCH2CH3 or N-C=N;and

R7b = cycloheptanyloxy, cyclopropyloxy, cyclopentanyloxy, cyclohexanyloxy or -N(R4b)R5b.

NB: Full definitions are given in the Definitions (Full Definitions) field.

INDEPENDENT CLAIMS are included for the following:

(1) a composition (C1) comprising (I);

(2) a medical device comprising a drug delivering or eluting member and (C1) disposed on or in the drug delivering or eluting member;

(3) a microarray comprising a gene expression profile generated from a cell type treated with (I); and

(4) an expression profile database comprising a patient identifying reference; and an expression profile for the patient generated by administering (I).

ACTIVITY - Cytostatic; Antiinflammatory; Vasotropic; Antiarteriosclerotic; Antidiabetic; Cardiovascular-Gen.; Immunosuppressive; Antiarteriosclerotic; Antiarthritic; Antirheumatic; Antiulcer; Gastrointestinal-Gen.; Osteopathic; Dermatological; Ophthalmological; Neuroprotective; Respiratory-Gen.; Vasotropic; Antiallergic; Antiasthmatic; Antipsoriatic; Antibacterial; Fungicide; Virucide; Vulnerary; Cerebroprotective; Hemostatic; Nephrotropic; Hepatotropic; Muscular-Gen.

MECHANISM OF ACTION - Glycated protein inhibitor/blocker; Smooth muscle proliferation inhibitor; Heparanase activity modulator/inhibitor.

(I) was tested for smooth muscle proliferation inhibition (SMC) activity using human aortic smooth muscle cells and smooth muscle cell proliferation assay. (I) showed SMC inhibition of grater than 70%.

USE - For treating unwanted cellular proliferation, inflammation mediated disease, hyperproliferative disease, modulating a glycosidase enzyme in a human or an animal (claimed). Also useful for treating pathophysiological conditions arising from inflammatory responses and vascular occlusive conditions characterized by smooth muscle proliferation e.g. restenosis and atherosclerosis, and diabetes, cardiovascular diseases, organ transplant sequellae, neointimal hyperplasia, transplant vasculopathy, cardiac allograft vasculopathy and arteriosclerosis; for treating and preventing cancer, autoimmune diseases, arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosis, antiphospholipid syndrome, iridocyclitis/uveitis/optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis, orchitis/vasectomy reversal procedures, allergic/atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococcemia, trauma/hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, alcohol-induced hepatitis, chronic inflammatory pathologies, Crohn's pathology, sickle cell anemia, diabetes, nephrosis,

atopic diseases, hypersensitity reactions, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphalaxis, dermatitis, pernicious anemia, hemolytic disesease, thrombocytopenia, graft rejection of any organ or tissue, kidney translplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynoud's disease, type B insulin-resistant diabetes, myasthenia gravis, -meditated cytotoxicity, type III hypersensitivity reactions, POEMS syndrome, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, anti-phospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, autoimmune hemolytic anemia, autoimmune hepatitis, idiopathic pulmonary fibrosis, scleroderma, diabetes mellitus, chronic active hepatitis, vitiligo, vasculitis, post-MI cardiotomy syndrome, contact dermatitis, hypersensitivity pneumonitis, granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemachromatosis, **alpha-1-antitrypsin** deficiency, diabetic retinopathy, hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hematophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, ankylosing spondylitis, Behcet's disease, bullous pemphigoid, cardiomyopathy, celiac sprue-dermatitis, chronic fatigue immune dysfunction syndrome, chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatricial pemphigoid, CREST syndrome, cold agglutinin disease, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, Graves' disease, Guillain-Barr, idiopathic thrombocytopenia purpura (ITP), IgA nephropathy, insulin dependent diabetes, lichen planus, meniere's disease, multiple sclerosis, pemphigus vulgaris, polyarteritis nodosa, Cogan's syndrome, polychondritis, polyglandular syndromes, polymyalgia rheumatica, polymyositis and dermatomyositis, primary agammaglobulinemia, Raynaud's phenomenon, Reiter's syndrome, rheumatic fever, stiff-man syndrome, Takayasu arteritis and temporal arteritis/giant cell arteritis.

Dwg.0/86

FS CPI EPI

FA AB; GI; DCN

MC CPI: B05-B01M; B06-H; B07-D13; B11-C04; B11-C08E6; B11-C09; B12-K04; B14-C03; B14-C04; B14-C06; B14-C09; B14-D01; B14-D07B; B14-E08; B14-E10C; B14-E11; B14-F01; B14-F02; B14-F03; B14-F07; B14-F08; B14-G02; B14-H01; B14-J01; B14-J05; B14-K01; B14-L06; B14-M01; B14-N01; **B14-N02**; B14-N03; B14-N04; B14-N07; B14-N10; B14-N11; B14-N12; B14-N13; B14-N14; B14-N16; B14-N17; B14-R02; B14-S01; B14-S04; B14-S06; D08-B; D09-C01

EPI: S05-G02G1; T01-J05B4P; T01-J06A1

TECH UPTX: 20041122

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: No general method for preparation of (I) is given.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Cell: The cell type is coronary artery, umbilical artery, umbilical vein, aortic, dermal microvascular, pulmonary artery or myometrium microvascular endothelium, keratinocyte, bronchial, mammary, prostate, renal cortical, renal proximal tubule, small

airway or renal epithelium, umbilical artery smooth muscle, neonatal dermal fibroblast, pulmonary artery smooth muscle, dermal fibroblast, neural progenitor cells, skeletal muscle, astrocytes, aortic smooth muscle, mesangial cells, coronary artery, bronchial or uterine smooth muscle, lung fibroblast, osteoblasts or prostate stromal cells.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: (C1) Further comprises a carrier and optionally auxiliary, preservative and excipient. (C1) further comprising an agent selected from a chemotherapeutic agent, immunosuppressive agent, cytokine, cytotoxic agent, nucleolytic compound, radioactive isotope, receptor, pro-drug activating enzyme, anti-inflammatory agent, antirheumatic agent, cardiovascular agent and/or toxin.

ABEX UPTX: 20041122

WIDER DISCLOSURE - Triazine compounds of formula (II) are also disclosure as new.

Na, Nb and Nc = pendant substituted amino group.

SPECIFIC COMPOUNDS - 162 Compounds are specifically claimed as (I) e.g. N-(3-chloro-4-methoxy-phenyl)-N'-cycloheptyl-N''-(1-ethyl-pyrrolidin-2-ylmethyl)-(1,3,5)triazine-2,4,6-triamine.

ADMINISTRATION - The drug delivering or eluting member is selected from a shunt, colostomy bag attachment device, **ear** drainage tube, lead for a pace maker, lead for an implantable defibrillator, suture, staple, anastornosis device, vertebral disk, bone pin, suture anchor, hemostatic barrier, clamp, screw, plate, clip, vascular implant, tissue adhesive, tissue sealant, tissue scaffold, bone substitute, intraluminal device, stent or vascular support (preferably stent). (C1) Is in the form of tablet, capsule, cachet, powder, granule, solution, suspension, emulsion, bolus, lozenge, suppository, pessary, tamport, cream, gel, paste, foam, spray, aerosol, microcapsule, liposome, transdermal patch, pastille, paste or mouthwash (claimed). Dosage of (I) is 0.1 - 100 mg and administered orally, corneal, conjunctivally, buccally, sublingually, nasally, vaginally, pulmonary, abdominally, intestinally, rectally or suppository.

EXAMPLE - To 6-chloro-N-(3-chloro-4-methoxy-phenyl)-N'-cycloheptyl-(1,3,5)triazine-2,4-diamine (0.1257 g) dissolved in acetonitrile (3 ml) was added N,N-diisopropylethylamine (DIEA) (0.07 ml) followed by 2-(aminomethyl)-1-ethyl pyrrolidine (0.06 ml). The mixture was refluxed overnight under a nitrogen atmosphere. After work-up N-(3-chloro-4-methoxy-phenyl)-N'-cycloheptyl-N-(1-ethyl-pyrrolidin-2-ylmethyl)-1,3,5)triazine-2,4,6-triamine (77 mg) was obtained.

DEFINITIONS - Full Definitions:

R1b = 3-X-4-methoxy-phenyl, 4-fluoro-5-methoxy-pyridin-2-yl, 3-fluoro-2-methoxy-pyridin-5-yl, 3-fluoro-4-(Na+ O-)-phenyl, 3-fluoro-4-(K+ O-)-phenyl, 3-(trifluoromethyl)-4-methoxyphenyl, 3-(trifluoromethyl)-4-(trifluoromethoxy)phenyl, 3-(trifluoromethyl)-4-hydroxyphenyl, 3-fluoro-4-Y-phenyl or 4-methoxy-3-carboxy-phenyl (or its sodium salt);

X = fluoro, chloro, bromo or iodo;

Y = methoxymethoxy, methylthiomethoxy, cyclopropyloxy, PO3-O-methoxy, di(tert-butoxy)-P(O)-O-methoxy, di(benzyloxy)-P(O)-O-methoxy, PO4, methoxyethoxyethoxyethoxyethylcarbonyloxy, hydroxyethoxyethoxyethoxyethylcarbonyloxy, hydroxyethoxyethoxyethoxyethoxy or methoxyethoxyethoxyethoxyethoxy;

R2b = hexahydro-pyrrolo(1,2-c)imidazol-2-yl, hexahydro-pyrrolo(1,2-c)imidazol-3-on-2-yl, 2,3-dihydro-1H-indol-1-yl, 1H-indol-1-yl, -NH-R3b, -N(CH3)-R3b or -O-R3b;

R3b = 1-Ra-pyrroldin-2-ylmethyl, 1-Rb-piperidin-4-yl, tetrahydrofuran-2-

yl, 1-ethyl-pyrrolidin-2-yl oxide, hexahydropyran-4-yl, 1-ethylpyrrolidinium-2-ylmethyl bromide, chloride, iodide, fumarate or succinate, 1-ethyl-1-methylcarbonylpyrrolidinium-2-ylmethyl chloride, 1-methyl-1-PO4CH2-pyrrolidinium-2-ylmethyl chloride or trifluoroacetate, 1-ethyl-1-(di(tert-butoxyor benzyloxy)P(O)-OCH2)-pyrrolidinium-2-yl methyl chloride, 1-methylpyrrol-2-ylmethyl, thiphen-2-ylmethyl, 1,1-dioxothiophen-2-ylmethyl, furan-2-yl, 2-ethyl, methyl, amino or hydroxy-cyclopentyl,3-hydroxycyclopentyl, imidazol-4-yl or pyridin-2 or 3-yl;
Ra = H, methyl, ethyl, C(O)H, COOH, C(O)NH2, hydroxyethoxyethoxyethoxyethoxyethylcarbonyl, methoxyethoxyethoxyethoxyethoxyethylcarbonyl, hydroxyethoxyethoxyethoxyethoxymethyl, methoxyethoxyethoxyethoxyethoxymethyl or PO4-CH2-;
Rb = COOH, C(O)NH2, C(O)CH3, H, methyl, amino, dimethylamino, ethylcarbonyl, propylcarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, hydroxy, methylcarbonylmethyl, ethylcarbonylmethyl, propylcarbonylmethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, propoxycarbonylmethyl or phenoxycarbonyl;
R4b = H, CH3, CH2CH3 or CH2CH2CH3;
R5b = cycloheptane, cyclohepten-4-yl, azepan-4-yl, 1-methyl-azepan-4-yl, thiepan-4-yl, thiepane 1,1-dioxid-4-yl, oxepan-2-yl, azepan-2-yl, thiepan-2yl, thiepan-3-yl, thiepane 1,1-dioxid-3-yl, azepan-1-yl, cyclohepten-3-yl, azepan-3-yl, oxepan-3-yl, azepan-2-on-3-yl, -CH(CH2CH3)CH2CH3, cyclopenten-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, tetrahydro-furan-3-yl, pyrrolidin-2-on-3-yl, cyclohexen-3-yl, tetrahydro-pyran-3-yl, piperidin-1-yl, piperidin-2-on-3-yl, -C=N, -C(O)CH3, -C(O)OH, -C(O)NH2, -CH2-C(O)CH3, -CH2-C(O)-CH2CH3, indo-1-aza-bicyclo(2.2.1)heptan-3-yl, exo-1-aza-bicyclo(2.2.1)heptan-3-yl or bicyclo(2.2.1)heptan-2-yl;
R6b = O, NH, NCH3, NCH2CH3 or N-C=N;and
R7b = cycloheptanyloxy, cyclopropyloxy, cyclopentanyloxy, cyclohexanyloxy or -N(R4b)R5b.

L151 ANSWER 6 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-542624 [52] WPIX
CR 2003-067606 [06]; 2003-606116 [57]; 2003-830575 [77]; 2003-830978 [77]; 2003-830979 [77]; 2003-899131 [82]; 2004-032631 [03]; 2004-059437 [06]; 2004-069282 [07]; 2004-551748 [53]; 2004-652054 [63]; 2004-708482 [69]
DNC C2004-199091
TI Use of an atomically disordered crystalline material or a nanocrystalline material comprising a metal and an element for the treatment of e.g., tuberculosis, pneumonia and cystic fibrosis.
DC B06
IN GILLIS, S H; SCHECHTER, P; STILES, J A R
PA (GILL-I) GILLIS S H; (SCHE-I) SCHECHTER P; (STIL-I) STILES J A R
CYC 1
PI US 2004131698 A1 20040708 (200452)* 42 A61K033-24
ADT US 2004131698 A1 CIP of US 2000-628735 20000727, CIP of US 2001-840637 20010423, CIP of US 2001-916757 20010727, CIP of US 2002-128208 20020423, CIP of US 2002-131509 20020423, CIP of US 2002-131511 20020423, CIP of US 2002-131568 20020423, CIP of US 2002-159587 20020530, CIP of US 2002-277298 20021022, CIP of US 2002-277320 20021022, CIP of US 2002-277356 20021022, CIP of US 2002-277358 20021022, CIP of US 2002-277362 20021022, CIP of US 2002-277673 20021022, US 2003-690724 20031022
FDT US 2004131698 A1 CIP of US 6692773
PRAI US 2003-690724 20031022; US 2000-628735 20000727;
US 2001-840637 20010423; US 2001-916757 20010727;
US 2002-128208 20020423; US 2002-131509 20020423;
US 2002-131511 20020423; US 2002-131568 20020423;

US 2002-159587 20020530; US 2002-277298 20021022;
US 2002-277320 20021022; US 2002-277356 20021022;
US 2002-277358 20021022; US 2002-277362 20021022;
US 2002-277673 20021022

IC ICM A61K033-24

AB US2004131698 A UPAB: 20041109
NOVELTY - Treatment of a condition comprises contacting an area of the condition with an atomically disordered crystalline material or a nanocrystalline material (I) (that contains at least one atomic percent of the element) comprising a metal and an element such as oxygen, nitrogen, carbon, boron, sulfur, halo, phosphorus, silicon and/or hydrogen.

ACTIVITY - Antibacterial; Antiinflammatory; Fungicide; Virucide; Immunosuppressive; Hemostatic; Cytostatic; Respiratory-Gen.; Antiasthmatic; Antimicrobial; Antitubercular; Tuberculostatic; Antiallergic; CNS-Gen.; Antiarthritic; Antiarteriosclerotic; Vasotropic; Antiangiogenic; Gastrointestinal-Gen.; Auditory; Ophthalmological; Dermatological; Vulnerary; Antiseborrheic; Antipsoriatic; Uropathic; Antipruritic.

(I) was assessed for its ability to control Propionibacterium acne by in vitro test. The results showed that (I) at 10 micro g/ml, gave 4.3 logarithm reduction in viable Propionibacterium acne counts in two hours.

MECHANISM OF ACTION - **Matrix metalloproteinases** modulator.

USE - (I) is useful to treat bacterial conditions, biofilm conditions, microbial conditions, inflammatory conditions, fungal conditions, viral conditions, autoimmune conditions, idiopathic conditions, hyperproliferative conditions, noncancerous growths and/or cancerous conditions of respiratory conditions (preferably asthma, emphysema, bronchitis, pulmonary edema, acute respiratory distress syndrome, bronchopulmonary dysplasia, fibrotic conditions, pulmonary atelectasis, tuberculosis, pneumonia, sinusitis, allergic rhinitis, pharyngitis, mucositis, stomatitis, chronic obstructive pulmonary disease, bronchiectasis and/or cystic fibrosis), a musculo-skeletal condition (preferably tendonitis, osteomyelitis, fibromyalgia, bursitis and/or arthritis), circulatory condition (preferably arteriosclerosis, lymphoma, septicemia, leukemia, ischemic vascular disease, lymphangitis and/or atherosclerosis), mucosal conditions and/or serosal conditions (preferably pericarditis, Bowen's disease, stomatitis, prostatitis, digestive disorders, peptic ulcers, esophageal ulcers, gastric ulcers, duodenal ulcer, espohagitis, gastritis, enteritis, enterogastric intestinal hemorrhage, toxic epidermal necrolysis syndrome, Stevens Johnson syndrome, fibrotic conditions, bronchitis, pharyngitis, common cold, **ear** infections, sore throat, sexually transmitted diseases, inflammatory bowel disease, colitis, hemorrhoids, thrush, dental conditions, oral conditions, conjunctivitis and/or periodontal conditions), cancer (particularly tumors and/or hematologic malignancies), skin conditions and integument conditions (preferably burn, eczema, erythroderma, an insect bite, mycosis fungoides, pyoderma gangrenosum, eythrema multiforme, rosacea, onychomycosis, acne, psoriasis, Reiter's syndrome, pityriasis rubra pilaris, hyperpigmentation, vitiligo, hypertropic scarring, keloid, lichen plainus, age related skin disorders and/or hyperproliferative variants of the disorders of keratinization) (claimed.)

Dwg.0/9

FS CPI

FA AB; DCN

MC CPI: B05-A03B; B05-C02; B14-A01; B14-A02; B14-A04; B14-C01; B14-C03; B14-C09; B14-D07; B14-E04; B14-E08; B14-E10; B14-F01; B14-F02; B14-F07; B14-F08; B14-G02D; B14-H01; B14-H01A; B14-J05; B14-K01; B14-L01; B14-N01; **B14-N02**; B14-N03; B14-N04; B14-N05; B14-N06B; B14-N17; B14-S06

TECH UPTX: 20040813
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The area of contact of (I), where apoptosis has to be induced is a hyperplastic tissue, a tumor tissue and/or a cancerous lesion. Apoptosis is induced by modulating **matrix metalloproteinases** at the area of the subject.
ABEX UPTX: 20040813
SPECIFIC COMPOUNDS - Silver is specifically disclosed as the metal. Silver nitrate is specifically disclosed as the crystalline material (I).

ADMINISTRATION - Administration of (I) is oral, parenteral, topical or by inhalation. No dosage is given.

L151 ANSWER 7 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-480798 [45] WPIX
DNN N2004-379260 DNC C2004-178833
TI Treatment of **otitis** media involves administration of protease inhibitor such as alpha one-antitrypsin.
DC B02 P32
IN ANTONELLI, P J; BARR, P J; PEMBERTON, P A; SCHULTZ, G S; SUNDIN, D J
PA (ANTO-I) ANTONELLI P J; (BARR-I) BARR P J; (PEMB-I) PEMBERTON P A; (SCHU-I) SCHULTZ G S; (SUND-I) SUNDIN D J; (ARRI-N) ARRIVA PHARM INC
CYC 107
PI WO 2004052236 A2 20040624 (200445)* EN 33 A61F000-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2004175383 A1 20040909 (200459) A61K039-395
AU 2003296378 A1 20040630 (200472) A61F000-00
ADT WO 2004052236 A2 WO 2003-US39053 20031208; US 2004175383 A1 Provisional US 2002-431286P 20021206, Provisional US 2002-435985P 20021220, US 2003-731375 20031208; AU 2003296378 A1 AU 2003-296378 20031208
FDT AU 2003296378 A1 Based on WO 2004052236
PRAI US 2002-435985P 20021220; US 2002-431286P 20021206; US 2003-731375 20031208
IC ICM A61F000-00; A61K039-395
ICS **A61K031-56**
AB WO2004052236 A UPAB: 20040716
NOVELTY - Treatment of **otitis** media in a mammal involves administering alpha one-antitrypsin (AAT).
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit comprising AAT and instructions for its use in the treatment of **otitis** media.
ACTIVITY - Auditory.
MECHANISM OF ACTION - Protease inhibitor.
The utility of recombinant alpha one-antitrypsin (rAAT) and **ilomastat** in treating **otitis** media was determined by measuring human neutrophil elastase activity using a standard technique in middle ear effusion samples. rAAT was expressed in recombinant yeast cells as described in Travis et. al., J. Biol. Chem 260:4384;4389(1985) and purified by column chromatography. The results showed inhibition (greater than 30% reduction) in 82% of the samples.
USE - The method is useful for treating **otitis** media (e.g. recurrent acute **otitis** media (RAOM), chronic **otitis** media with effusion (COME), acute post-tympanostomy otorrha (APTO), chronic suppurative **otitis** media (CSOM) or choleastoma) in mammal (preferably human) having perforated tympanic membrane due to

tympanostomy (all claimed).
ADVANTAGE - The lack of toxicity of AAT and **ilomastat** allows direct application to the site of infection. The method reduces the risk, severity and/or increase the time to possible consequences of tube insertion, including post-tympanostomy tube otorrha and/or the necessity of tube replacement.
Dwg.0/0
FS CPI GMPI
FA AB; DCN
MC CPI: **B04-J02**; B04-N06; B06-D01; B14-A01; B14-C03; B14-D07C; **B14-N02**
TECH UPTX: 20040716
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method additionally involves administering antibiotic, steroid or **ilomastat.**
ABEX UPTX: 20040716
ADMINISTRATION - Dosage is 0.1 - 50 mg. Administration is in the form of liquid or dry powder (claimed), topical, by insufflation, otical, oral, simultaneous or nasal.

EXAMPLE - No relevant example given.

L151 ANSWER 8 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-440892 [41] WPIX
DNC C2004-165261
TI Composition useful for treating and preventing inflammatory or hyperproliferative mucocutaneous disorder comprises protease inhibitor and gelling agent.
DC A96 B04 D16
IN ANGEL, A J; BARR, P J; BATHURST, I C; MAYHEW, J W; PEMBERTON, P A; SUNDIN, D J
PA (ARRI-N) ARRIVA-PROMETIC INC
CYC 107
PI WO 2004045634 A1 20040603 (200441)* EN 51 A61K038-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003286258 A1 20040615 (200470) A61K038-00
ADT WO 2004045634 A1 WO 2003-GB5049 20031120; AU 2003286258 A1 AU 2003-286258 20031120
FDT AU 2003286258 A1 Based on WO 2004045634
PRAI US 2002-427702P 20021120
IC ICM A61K038-00
AB WO2004045634 A UPAB: 20040629
NOVELTY - A composition (C1) comprises protease inhibitor (a) and gelling agent (b).
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for preparation (M1) of a protease inhibitor gel composition involving:
(1) mixing a powdered gelling agent with an aqueous solution to form a gel;
(2) adjusting pH of the gel to 5.5 - 9;
(3) sterilizing the gel; and
(4) combining a protease inhibitor with the gel to form the protease inhibitor gel.
ACTIVITY - Cytostatic; Antiinflammatory; Dermatological; Antiulcer; Antiseborrheic; Antipsoriatic; Antilichen; Anti-HIV; Keratolytic;

Ophthalmological; Gastrointestinal-Gen.; Auditory; Antiasthmatic; Vulnerary.

MECHANISM OF ACTION - Protease inhibitor.

USE - For treating or preventing inflammatory or hyperproliferative mucocutaneous disorder; dermatological disorder (e.g. atopic dermatitis, skin photodamge, extrinsic skin aging, skin irritation, chronic, burn and ulcer wounds, acne, psoriasis, lichen (particularly lichen planus), basal or squamous cell carcinoma (Bowen's disease), Kaposi's sarcoma, keratosis, disorder of keratinization such as ichthyosis (particularly lamellar ichthyosis) and keratoderma), disorder of the **ear** and ocular disorder such as **otitis**, conjunctivitis, disorders of the gastrointestinal tract and urinary tract such as colitis and interstitial cystitis (claimed); disorder of lung e.g. inflammation of the lung mucosa such as asthma.

ADVANTAGE - The gel formulations maintain a uniform pH and have demonstrated improved protease inhibitor solubility, gel consistency, sterility and an unexpectedly superior therapeutic activity and stability with no undesirable side effects.

Dwg.0/2

FS CPI

FA AB; DCN

MC CPI: A12-V01; B04-N02; B12-M07; B14-C03; B14-D07C; B14-E10C; B14-H01; B14-K01A; **B14-N02**; B14-N03; B14-N07B; B14-N17; D05-C12

TECH UPTX: 20040629

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The aqueous solution is a physiological buffer. (M1) Further involves adjusting the pH of the protease inhibitor gel from 5.5 - 9 and lyophilizing the protease inhibitor gel. The sterilizing involves irradiation.

Preferred Composition: (C1) Further comprises a physiological buffer at pH of 6 - 9 (preferably 6.5 - 7.5) and at least one agent.

Preferred Components: (a) Is an **alpha 1-antitrypsin** (preferably natural, synthetic or recombinant **alpha 1-antitrypsin**, modified peptide, biologically active fragment, substantially homologous polypeptide, oligopeptide, homodimer, heterodimer, variant, derivative and/or **alpha 1-antitrypsin** analog).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: (b) Is hydroxyethyl cellulose, hydroxypropyl cellulose, polyacrylic acid and/or polyoxyethylene-polyoxypropylene block copolymer.

ABEX UPTX: 20040629

ADMINISTRATION - Dosage is 0.5 - 100 mg/kg. The sterile composition may be administered by transdermal, intraperitoneal, intracranial, intravaginal, intrauterine, oral, rectal, ophthalmic (including intravitreal or intracameral), nasal, topical (including subcutaneous, intraperitoneal, intramuscular, intradermal, intratracheal or epidural).

EXAMPLE - A composition comprised (weight/weight%): antitrypsin (10), benzyl alcohol (1), hydroxyethyl cellulose (2) and purified water (97). The composition was tested after two weeks and was found to be clear and had pH of 7.45.

L151 ANSWER 9 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2004-375816 [35] WPIX

DNC C2004-141291

TI Use of metal containing material for prophylactic treatment of a condition e.g. bacterial, biofilm, microbial, inflammatory and fungal conditions.

DC B05

IN DEMLING, R H; GILLIS, S H; SCHECHTER, P

PA (DEML-I) DEMLING R H; (GILL-I) GILLIS S H; (SCHE-I) SCHECHTER P; (NUCF-N) NUCFRYST PHARM CORP

CYC 106
PI WO 2004037186 A2 20040506 (200435)* EN 73 A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG
PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ
VC VN YU ZA ZM ZW
US 2004110738 A1 20040610 (200438) A61K031-555
AU 2003286575 A1 20040513 (200468) A61K000-00
ADT WO 2004037186 A2 WO 2003-US33431 20031022; US 2004110738 A1 Provisional US 2002-420167P 20021022, US 2003-690710 20031022; AU 2003286575 A1 AU 2003-286575 20031022
FDT AU 2003286575 A1 Based on WO 2004037186
PRAI US 2002-420167P 20021022; US 2003-690710 20031022
IC ICM A61K000-00; A61K031-555
ICS A61K031-28; A61K033-24
AB WO2004037186 A UPAB: 20040603
NOVELTY - Prophylactic treatment comprises contacting a first area (A) of a subject with a metal containing material (I) to reduce the occurrence of a condition at a second area (B). (A) is different from (B).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of prophylactic treatment of a condition comprising contacting an object with (I) to reduce the occurrence of a condition at an area of a subject.

ACTIVITY - Antibacterial; Antimicrobial; Antiinflammatory; Fungicide; Dermatological; Virucide; Immunosuppressive; Cytostatic; Vulnerary; Antiseborrheic; Antipsoriatic; Ophthalmological; Uropathic; Antipruritic; Antiasthmatic; Respiratory-Gen.; Neuroprotective; Antitubercular; Tuberculostatic; CNS-Gen.; Muscular-Gen.; Osteopathic; Antiarthritic; Vasotropic; Antiarteriosclerotic; Antiallergic; Gastrointestinal-Gen.; Antiulcer; Auditory.

Test details are described but no results given.

MECHANISM OF ACTION - **Matrix Metalloproteinase** Modulator.

USE - (I) is useful for the prophylactic treatment of the conditions of bacterial, biofilm, microbial, inflammatory, fungal, viral, autoimmune , hyperproliferative, idiopathic or cancerous conditions (preferably non-bacterial conditions) such as skin, integument conditions (burn, eczema, erythroderma, an insect bite, mycosis fungoides, pyoderma gangrenosum, eythrema multiforme, rosacea, onychomycosis, acne, psoriasis, Reiter's syndrome, pityriasis rubra pilaris, hyperpigmentation, vitiligo, scarring conditions, keloid, lichen planus, age related skin disorders or hyperproliferative variants of the disorders of keratinization), respiratory conditions (asthma, emphysema, bronchitis, pulmonary edema, acute respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary fibrosis, pulmonary atelectasis, tuberculosis, pneumonia, sinusitis, allergic rhinitis, pharyngitis, mucositis, stomatitis, chronic obstructive pulmonary disease, bronchiectasis, lupus pneumonitis, cystic fibrosis or nosocomial or ventilator associated pneumonia), musculo-skeletal condition (tendonitis, osteomyelitis, fibromyalgia, bursitis or arthritis), circulatory condition (arteriosclerosis, lymphoma, septicemia, leukemia, ischemic vascular disease, lymphangitis or atherosclerosis), cancer (tumors or hematologic malignancies) and mucosal conditions or serosal conditions (pericarditis, Bowen's disease, stomatitis, prostatitis, sinusitis, allergic rhinitis, digestive disorders, peptic ulcers, esophageal ulcers, gastric ulcers, duodenal ulcers, toxic epidermal necrolysis syndrome, Stevens Johnson syndrome, bronchitis, pneumonia, pharyngitis, common cold, **ear** infections, sore throat, sexually

transmitted diseases, inflammatory bowel disease, colitis, hemorrhoids, thrush, dental conditions, oral conditions, conjunctivitis or periodontal conditions) (claimed).
Dwg.0/1
FS CPI
FA AB; DCN
MC CPI: B05-A03B; B05-C02; B05-C04; B05-C08; B07-D12; B10-C02; B10-C04D; B10-C04E; B12-M01B; B12-M01D; B12-M07; B12-M08; B12-M11B; B12-M11C; B12-M11F; B12-M11G; B14-A01; B14-A01B1; B14-A02; B14-A04; B14-C01; B14-C03; B14-C09; B14-D07C; B14-E04; B14-E08; B14-E10; B14-E10C; B14-F01; B14-F02; B14-F02D; B14-F02E; B14-F07; B14-G02D; B14-H01; B14-J05; B14-K01; B14-L01; **B14-N02**; B14-N03; B14-N04; B14-N06B; B14-N07A; B14-N17; B14-S06
TECH UPTX: 20040603
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The treatment further comprises recognizing a possibility for occurrence of the condition at (B) and selecting (A) (hyperplasic tissue, tumor tissue or cancerous lesion but not the skin and is preferably a portion of the respiratory system, musculo-skeletal system, circulatory system, gastrointestinal system, sublingual area or subdermal area) for contact with the (I) to reduce occurrence of the condition at (B) (hyperplasic tissue, tumor tissue or cancerous lesion). (B) is substantially free of or has the condition when (A) is contacted with the (I). (A) is substantially free of or has the condition when contacted with (I). The treatment prophylactically induces apoptosis and prophylactically modulates **matrix metalloproteinase** at (B). The treatment further comprises the formation of solution containing (I) into an aerosol and inhalation of the solution. (I) has a prophylactic ratio of about 0.95 or less for the condition. (A) and (B) can also be the same area. The treatment with the object after contacting the object with (I) further comprises the contact of the object with the subject (different area of the subject), transferring (I) directly from the object to the subject. The material transferred to the subject comprises a therapeutic agent. Preferred Components: (A) comprises a mucosal membrane (oral or nasal cavity) and (B) comprises the subjects lungs. (I) is a metal (silver (preferred), gold, platinum, palladium and/or combinations) (preferably silver nitrate, silver hydroxide, silver sulfadiazine, colloidal silver, silver carbonate, silver oxide, silver acetate, silver lactate, silver citrate, silver succinate, silver sorbate, silver myristate, silver stearate, silver oleate, silver glutonate, silver adipate or alkali silver thiosulfate) or alloy. (I) comprises an anionic material, atom, molecule, cluster, an atomically disordered crystal containing material or noncrystalline containing material (antimicrobial, anti-biofilm, antibacterial, anti-inflammatory, antifungal, antiviral, anti-autoimmune, anti-cancer or pro-apoptosis metal-containing materials, anti-proliferative materials, **matrix metalloprotienase**, modulating metal-containing materials and/or combinations). (I) (0.001 (preferably 10) wt.% or less) is in a solution comprising a solvent or is in the form of a free standing powder, carrier, powder impregnated material, swab, foam, liposome, tape, pill, capsule, tablet, suppository or lozenge and not in the form of a dressing.
ABEX UPTX: 20040603
ADMINISTRATION - Administration of (I) is by injection or inhalation. No dosage given.

L151 ANSWER 10 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-203401 [19] WPIX
DNC C2004-080079
TI New tetracycline compounds useful for treatment of bacterial infections and neurodegenerative disorders e.g. Alzheimer's disease and dementia.

DC B02 B05
IN BANDARAGE, U; CHEN, J; ISMAIL, M Y; NELSON, M L; SIZENSKY, E; CHEMENG, K; KIM, O
PA (PARA-N) PARATEK PHARM INC
CYC 105
PI WO 2004006850 A2 20040122 (200419)* EN 43 A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
AU 2003261161 A1 20040202 (200450) A61K000-00
EP 1534300 A2 20050601 (200536) EN A61K031-65
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
ADT WO 2004006850 A2 WO 2003-US21992 20030714; AU 2003261161 A1 AU 2003-261161 20030714; EP 1534300 A2 EP 2003-764630 20030714, WO 2003-US21992 20030714
FDT AU 2003261161 A1 Based on WO 2004006850; EP 1534300 A2 Based on WO 2004006850
PRAI US 2002-395696P 20020712
IC ICM A61K000-00; A61K031-65
AB WO2004006850 A UPAB: 20040318
NOVELTY - Tetracycline compounds (I) are new.
DETAILED DESCRIPTION - Tetracycline compounds of formula (I), their salts, esters and enantiomers are new.
X = CHC(R13Y'Y), C=CR13Y, CR6aR6, S, NR6 or O;
R2b = C(O)NR2R2a or CN;
R2, R2a = Q1;
Q1 = H, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclyl, heteroaryl or a prodrug group;
R12a = OR12 or NR12R12b;
R3, R10, R11, R12, R12b = H, alkyl, alkenyl, aryl, alkynyl, aralkyl, acetyl, alkylcarbonyl, alkenylcarbonyl, arylcarbonyl, alkynylcarbonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkynylaminocarbonyl, arylaminocarbonyl, alkylthiocarbonyl, alkenylthiocarbonyl, alkynylthiocarbonyl, arylthiocarbonyl, alkyloxythiocarbonyl, alkenyloxythiocarbonyl, alkynyloxythiocarbonyl, aryloxythiocarbonyl, alkylaminothiocarbonyl, alkenylaminothiocarbonyl, alkynylaminothiocarbonyl, arylaminothiocarbonyl, alkylthiothiocarbonyl, alkenylthiothiocarbonyl, alkynylthiothiocarbonyl or arylthiothiocarbonyl;
R4, R4a = NR40R41, alkyl, alkenyl, alkynyl, hydroxy, halo or H, or R4 + R4a = =O;
R5 = OH, H, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkylcarbonyloxy or arylcarbonyloxy;
R6, R6a = H, methylene, absent, OH, halo, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino or arylalkyl;
R7 = T1 or (CH2)0-3NR7cC(=W')WR7a;
T1 = H, OH, halo, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylalkyl, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocyclyl or thionitroso;
R8 = H, OH, halo, thiol, nitro, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, amino, arylalkenyl, arylalkynyl, acyl, aminoalkyl, heterocyclyl, thionitroso or (CH2)0-3NR8cC(=E')ER8a;

R9 = T1 or (CH2)0-3NR9cC(=Z')ZR9a;

R13 = H, OH, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, alkylsulfinyl, alkylsulfonyl, alkylamino or arylalkyl;

E = CR8dR8e, S, NR8b or O;

E' = O, NR8f or S;

W = CR7dR7e, S, NR7b or O;

W' = O, NR7f or S;

Y', Y = H, OH, halo, CN, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino or arylalkyl;

Z = CR9dR9e, S, NR9b or O;

Z' = O, S or NR9f, and

R7a-R7f, R8a-R8f, R9a-R9e = Q1 or acyl,

provided that at least one of R3, R10, R11 or R12 is not H when R2 = C(=O)NR2R2a and R12a is OR12 (sic).

ACTIVITY - Antiinflammatory; Cytostatic; Ophthalmological; Cerebroprotective; Vasotropic; Neuroprotective; Nootropic; Anticonvulsant; Antiparkinsonian; Virucide; Fungicide; Antiarthritic; Osteopathic; Antidiabetic; Antidiarrheic; Uropathic; Dermatological; Vulnerary; Antimalarial; Cardiant; Antiarteriosclerotic; Antiulcer; Ophthalmological; Respiratory-Gen.; Antirheumatic; Endocrine-Gen.; Antithyroid; Antibacterial; Gastrointestinal-Gen.; Neuroleptic; Hypotensive; Hypnotic; Antidepressant; Antimanic; Tranquilizer; Antimigraine; Anorectic; Antiasthmatic; CNS-Gen.

Test details are described but no results are given.

MECHANISM OF ACTION - None given.

USE - Used for treating a tetracycline responsive state, particularly inflammatory process associated state, cancer, lung injury, eye disorder, stroke, neurological disorder (e.g. Alzheimer's disease, Huntington's disease, Parkinson's disease, amylotropic lateral sclerosis and multiple sclerosis) (all claimed), viral and fungal infections (including those which are resistant to other tetracycline compounds), arthritis, osteoporosis, diabetes (e.g. diabetes I and diabetes II), diarrhea, urinary tract infections, infections of skin and skin structure, ear, nose and throat infections, wound infections, mastitis, nitric oxide associated states, particularly malaria, senescence, diabetes, vascular stroke, cardiac disease (reperfusion-associated injury following infarction), juvenile diabetes, matrix metalloproteinase states, particularly arteriosclerosis, corneal ulceration, emphysema, osteoarthritis, multiple sclerosis, osteosarcoma, osteomyelitis, bronchiectasis, chronic pulmonary obstructive disease, skin and eye disease, periodontitis, osteoporosis, rheumatoid arthritis, ulcerative colitis, inflammatory disorders, tumor growth and invasion, metastasis, acute and chronic lung injury, stroke, ischemia, ischemic stroke, diabetes, aortic or vascular aneurysms, skin tissue wounds, dry eye, bone and cartilage degradation), bone mass disorder, particularly osteoporosis, bone fractures, bone formation associated with surgical procedures such as facial reconstruction, osteogenesis imperfecta, hypophosphatasia, Paget's disease, fibrous dysplasia, osteopetrosis, myeloma bone disease and the depletion of calcium in bone such as that which is related to primary hyperparathyroidism, aortic or vascular aneurysm in vascular tissue and bacterial infections caused by e.g. Klebsiella pneumoniae.

The inflammatory disorders include osteoarthritis, acute and chronic infections (bacterial and fungal infections including diphtheria and pertussis), acute and chronic bronchitis, sinusitis, upper respiratory infections (e.g. common cold), acute and chronic gastroenteritis and colitis, acute and chronic cystitis and urethritis, acute and chronic dermatitis, acute and chronic conjunctivitis, acute and chronic serositis , particularly pericarditis, peritonitis, synovitis, pleuritis and tendonitis, uremic pericarditis, acute and chronic cholecystis, acute and chronic vaginitis, acute and chronic uveitis, drug reactions, insect

bites, burns (e.g. thermal, chemical and electrical) and sunburn.

The neurological disorders include Pick's disease, Lewy diffuse body diseases, senile dementia, Gilles de la Tourette's syndrome, progressive supranuclear palsy, epilepsy, Creutzfeldt-Jakob disease, autonomic function disorders, particularly hypertension and sleep disorders, neuropsychiatric disorders, particularly depression, schizophrenia, schizoaffective disorders, Korsakoff's psychosis, mania, anxiety disorders or phobic disorders, learning and memory disorders, particularly amnesia or age related memory loss, attention deficit disorder, dysthymic disorder, major depressive disorder, mania, obsessive compulsive disorder, psychoactive substance use disorder, anxiety, phobia, panic disorder, bipolar affective disorder, particularly mood disorder, and bipolar affective neurological disorders, particularly migraine and obesity. The acute lung injury includes adult respiratory distress syndrome, post-pump syndrome and trauma. The chronic lung disorders include asthma, cystic fibrosis and emphysema.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B02-T; B14-A01; B14-A02; B14-C01; B14-C03; B14-C09A; B14-C09B; B14-D02B; B14-E02; B14-E10C; B14-E12; B14-F02B; B14-F02D; B14-F07; B14-G02A; B14-H01; B14-H02; B14-J01A1; B14-J01A3; B14-J01A4; B14-J01B2; B14-J01B3; B14-J01B4; B14-J05; B14-J07; B14-K01A; B14-K01D; B14-K01F; B14-N01; **B14-N02**; B14-N03; B14-N04; B14-N05; B14-N06B; B14-N07B; B14-N10; B14-N12; B14-N14; B14-N16; B14-N17A; B14-N17B; B14-N17C; B14-S01; B14-S04; B14-S06

TECH UPTX: 20040318

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: No general preparation is given.

ABEX UPTX: 20040318

SPECIFIC COMPOUNDS - 22 Compounds (I) are specifically claimed e.g: 3-benzyloxysancycline (Ia).

ADMINISTRATION - The dosage is 0.01-100 (preferably 0.1-50, especially 1-20) mg/kg/day orally, topically, parenterally (e.g. intraperitoneally, subcutaneously, intravenously, intradermally, intraarticularly or intramuscularly) or enterally.

EXAMPLE - Sodium hydride (60%) in a mineral oil dispersion (100 mg) was added in small portions to a stirred solution of sancycline (0.5 g) in dimethylformamide (5 ml) at room temperature. The resulting suspension was stirred at room temperature for 5 minutes. Benzyl bromide (0.143 ml) was added and heated at 60degreesC for 16 hours. The reaction mixture was then cooled to room temperature and subjected to basic work up to obtain 3-benzyloxysancycline (Ia).

L151 ANSWER 11 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2003-830979 [77] WPIX

CR 2002-315278 [35]; 2003-058682 [05]; 2003-058683 [05]; 2003-067606 [06]; 2003-075604 [07]; 2003-140141 [13]; 2003-606116 [57]; 2003-754943 [71]; 2003-830575 [77]; 2003-830978 [77]; 2003-899131 [82]; 2004-032631 [03]; 2004-059437 [06]; 2004-069282 [07]; 2004-542624 [52]; 2004-551748 [53]; 2004-652054 [63]; 2004-708482 [69]

DNC C2003-234116

TI Treatment of a condition e.g. bacterial condition, microbial condition and inflammatory condition, involves contacting the condition with solution containing atomically disordered, nanocrystalline metal-containing compound.

DC B06 D21 D22

IN BURRELL, R E; GILLIS, S H; LAM, K; MOXHAM, P H; NAYLOR, A G; SCHECHTER, P;

WRIGHT, J B; YIN, H Q
PA (BURR-I) BURRELL R E; (GILL-I) GILLIS S H; (LAMK-I) LAM K; (MOXH-I) MOXHAM P H; (NAYL-I) NAYLOR A G; (SCHE-I) SCHECHTER P; (WRIG-I) WRIGHT J B; (YINH-I) YIN H Q
CYC 1
PI US 2003180379 A1 20030925 (200377)* 42 A61K033-38
ADT US 2003180379 A1 CIP of US 2000-628735 20000727, CIP of US 2001-840637 20010423, CIP of US 2001-916757 20010727, CIP of US 2002-128208 20020423, CIP of US 2002-131509 20020423, CIP of US 2002-131511 20020423, US 2002-277673 20021022
PRAI US 2002-277673 20021022; US 2000-628735 20000727;
US 2001-840637 20010423; US 2001-916757 20010727;
US 2002-128208 20020423; US 2002-131509 20020423;
US 2002-131511 20020423
IC ICM A61K033-38
ICS A61K033-24; A61K033-26
AB US2003180379 A UPAB: 20041027
NOVELTY - Treatment of a subject having a condition e.g. bacterial condition; microbial condition and inflammatory condition, involves contacting an area of the subject having the condition with a solution containing an atomically disordered, nanocrystalline metal-containing compound.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a solution, comprising the atomically disordered, nanocrystalline metal-containing compound; and a solvent for the metal-containing compound. The metal containing compound is at least partially dissolved in the solvent (preferably water);

(2) an aerosol comprising a nanocrystalline, metal-containing compound;

(3) an aerosol comprising an atomically disordered, metal-containing a compound; and

(4) a method (M1) of treating a subject having a condition e.g. bacterial condition, microbial condition and inflammatory condition, involving contacting an area of the subject having the condition with the atomically disordered, crystalline metal-containing compound by injecting a solution containing the nanocrystalline metal-containing compound.

ACTIVITY - Dermatological; Antibacterial; Antiinflammatory; Fungicide; Virucide; Immunosuppressive; Cytostatic; Vulnerary; Insecticide; Antiseborrheic; Antipsoriatic; Ophthalmological; Uropathic; Antipruritic; Respiratory-Gen.; Antiasthmatic; Antitubercular; Tuberculostatic; CNS-Gen.; Antiarteriosclerotic; Endocrine-Gen.; Vasotropic; Cardiovascular-Gen.; Anti-HIV; Osteopathic; Antiarthritic; Antirheumatic; Gynecological; Immunomodulator; Gastrointestinal-Gen.; Antiulcer.

The antipsoriatic activity of nanocrystalline silver (a) was tested by using a female (58 year old) with psoriatic plaques. (a) Was deposited on sheets of high density polyethylene (HDPE) using a vapor deposition process. Two sheets of this coated HDPE were laminated together around a core of non-woven rayon polyester. A piece (50 multiply 50 mm) of this composite material was saturated with water and placed centrally on a one and a half year old (150 multiply 100 mm) psoriatic plaque on the patient's flank. The nanocrystalline silver coated material was covered with a piece of low moisture vapor transmission thin polymer film. The polymer sheet extended 50 mm beyond the nanocrystalline silver coated HDPE to provide control data regarding occlusion of the psoriatic plaque. The dressing was removed after three days. There was no discernible change in the plaque at this time. Two days later the area that was covered with the nanocrystalline silver had the appearance of normal skin while the rest of the plaque was still rough and unchanged including the untreated.

MECHANISM OF ACTION - Apoptosis inducer; **Matrix**

metalloproteinases modulator.

USE - The method is used for treating a condition e.g. skin conditions and integument conditions (e.g. bacterial, microbial, inflammatory, fungal, viral, autoimmune, idiopathic, noncancerous growths, cancerous conditions, burn, eczema, erythroderma, an insect bite, mycosis fungoides, pyoderma gangrenosum, eythrema multiforme, rosacea, onychomyocosis, acne, psoriasis, Reiter's syndrome, pityriasis rubra pilaris, hyperpigmentation, vitiligo, hypertropic scarring, keloid, lichen planus, age related skin disorders and hyperproliferative variants of the disorders of keratinization), respiratory condition (e.g. viral respiratory conditions, asthma, emphysema, bronchitis, pulmonary edema, acute respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary fibrosis, pulmonary atelectasis, tuberculosis, pneumonia, sinusitis, pharyngitis, mucositis, stomatitis, chronic obstructive pulmonary disease, bronchiectasis, lupus pneumonitis and cystic fibrosis), musculo-skeletal condition (e.g. tendonitis, osteomyelitis, fibromyalgia, bursitis and arthritis), circulatory condition (e.g. fungal circulatory conditions, arteriosclerosis, septicemia, leukemia, ischemic vascular disease, lymphangitis and atherosclerosis), cancer (e.g. tumors and hematologic malignancies), mucosal conditions and serosal conditions (e.g. pericarditis, Bowen's disease, stomatitis, prostatitis, sinusitis, digestive disorders, toxic epidermal necrolysis syndrome, Stevens Johnson syndrome, common cold, **ear** infections, sore throat, sexually transmitted diseases, inflammatory bowel disease, colitis, hemorrhoids, thrush, dental conditions, oral conditions, conjunctivitis, and periodontal conditions) (all claimed). Also for treating skin aging, keratoconus, restenosis, osteoarthritis, rheumatoid arthritis, degenerative joint disease, bone disease, wounds, hypovolemic shock, epidermolysis bullosa, scleritis, vascular leakage syndrome, collagenase induced disease, adhesions of the peritoneum, strictures of the esophagus or bowel, cachexia, HIV-infection and cardiovascular conditions, esophageal ulcer, gastric ulcer, duodenal ulcer, espohagitis, gastritis, enteritis, enterogastric intestinal hemorrhage and sexually transmitted disease (e.g. syphilis, gonorrhea, herpes, genital warts and chlamydia).

ADVANTAGE - The method induces apoptosis or modulates **matrix metalloproteinases** at the area of the subject.

Dwg.0/9

FS CPI

FA AB; DCN

MC CPI: B05-A03B; B14-A01; B14-A02; B14-A04; B14-C03; B14-C09; B14-D07C; B14-E08; B14-E10; B14-F01; B14-F02; B14-F07; B14-F08; B14-G02D; B14-H01; B14-H03; B14-J05; B14-K01; B14-N01; **B14-N02**; B14-N03; B14-N04; B14-N05; B14-N06B; B14-N07C; B14-N17; B14-R01; B14-S06; D08-B09A1; D08-B09A3; D09-A01

TECH UPTX: 20031128

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method additionally involves forming the solution containing the metal-containing compound; and contacting the solution within at most 1 or after 1.5 minutes of formation, to the area of the subject.

The method additionally involves either forming the solution by combining a powder of the metal-containing compound in a solvent; or forming the solution by disposing an article containing the metal-containing compound in a solvent.

The article comprises a substrate having a coating of the metal-containing compound disposed on it.

The method additionally involves forming the solution into an aerosol; inhaling the aerosol; and contacting the area of the subject includes injecting the solution into the subject.

The solution is injected with a needle less injector or with a needle.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The metal-containing compound is metal (preferably silver, gold, platinum or palladium; especially silver) or alloy (preferably metal oxide, metal nitride, metal boride, metal halide or metal hydride).
The metal-containing compound is an ionic compound.
The metal-containing compound comprises atom, molecule or cluster, or an antimicrobial compound.
The solution contains metal-containing compound (at least 0.001 or at most 10 wt.%).
The solution in the treatment additionally comprises a solvent.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: The area of the subject is hyperplastic tissue, tumor tissue or cancerous lesion.

ABEX UPTX: 20031128
ADMINISTRATION - The metal-containing compound is administered orally, nasally or by inhalation. No dosage given.

EXAMPLE - No relevant example given.

L151 ANSWER 12 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-830978 [77] WPIX
CR 2002-315278 [35]; 2003-058682 [05]; 2003-058683 [05]; 2003-067606 [06]; 2003-075604 [07]; 2003-140141 [13]; 2003-606116 [57]; 2003-754943 [71]; 2003-830575 [77]; 2003-830979 [77]; 2003-899131 [82]; 2004-032631 [03]; 2004-059437 [06]; 2004-069282 [07]; 2004-542624 [52]; 2004-551748 [53]; 2004-652054 [63]; 2004-708482 [69]
DNC C2003-234115
TI Use of free standing powder of a nanocrystalline metal-containing compound for the treatment of e.g. burns, acne, arteriosclerosis, asthma, psoriasis, cancer, hemorrhoids, colitis and viral, fungal and bacterial infections.
DC B04 B06 C03 D21 D22
IN BURRELL, R E; GILLIS, S H; SCHECHTER, P; LAM, K; MOXHAM, P H; NAYLOR, A G; WRIGHT, J B; YIN, H Q
PA (BURR-I) BURRELL R E; (GILL-I) GILLIS S H; (SCHE-I) SCHECHTER P; (NUCR-N) NUCRYST PHARM CORP
CYC 106
PI US 2003180378 A1 20030925 (200377)* 41 A61K033-38
WO 2004037187 A2 20040506 (200430) EN A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT US 2003180378 A1 CIP of US 2000-628735 20000727, CIP of US 2001-840637 20010423, CIP of US 2001-916757 20010727, CIP of US 2002-128208 20020423, CIP of US 2002-131509 20020423, CIP of US 2002-131511 20020423, CIP of US 2002-131568 20020423, CIP of US 2002-159587 20020530, US 2002-277298 20021022; WO 2004037187 A2 WO 2003-US33446 20031022
PRAI US 2002-277298 20021022; US 2000-628735 20000727;
US 2001-840637 20010423; US 2001-916757 20010727;
US 2002-128208 20020423; US 2002-131509 20020423;
US 2002-131511 20020423; US 2002-131568 20020423;
US 2002-159587 20020530; US 2002-277320 20021022;
US 2002-277356 20021022; US 2002-277358 20021022;
US 2002-277362 20021022; US 2002-277673 20021022;
US 2003-364983 20030212
IC ICM A61K000-00; A61K033-38

ICS A61K033-24
AB US2003180378 A UPAB: 20041027
NOVELTY - Treatment of diseases e.g. autoimmune conditions involves injecting or inhaling a free standing powder of a nanocrystalline metal-containing compound.

ACTIVITY - Antimicrobial; Antibacterial; Anti-inflammatory; Fungicide; Immunosuppressive; Cytostatic; Dermatological; Vulnerary; Antipsoriatic; Antiasthmatic; Respiratory-Gen.; Tuberculostatic; Auditory; Ophthalmological; Antiarteriosclerotic; Gastrointestinal-Gen.; Antiseborrheic; Uropathic; Antipruritic; Antitubercular; CNS Gen.; Antiarthritic; Vasotropic; Virucide.

The antiinflammatory activity of nanocrystalline derived silver solution (S1) (containing 400 ppm of Ag) was evaluated in rats. Pseudomonas aeruginosa (strain 5888) suspension (400 mu l) was intrathecally administered into the bronchi of each rat. A solution of silver nitrate (400 ppm) in deionized water was used as control. The rats were then dosed with (S1) through nebulizer for 2 - 2.5 hours. The rats were again dosed with (S1) 3 times a day for additional 1.5 days. The lungs from sacrificed rats were histopathologically analyzed. The lungs were normal to slightly inflamed/moderately to severely inflamed in rats treated with (S1)/control solution respectively. The results showed that (S1) had pulmonary anti-inflammatory activity.

MECHANISM OF ACTION - Microbial growth inhibitor. The microbial growth inhibitory efficacy of a silver solution derived from Aticoat (RTM; burn dressing) was evaluated against Pseudomonas aeruginosa (A). Mueller-Hinton agar plates streaked with (A) were exposed to nebulized silver solution. The plates were then incubated at 35 deg. C for 16 hours. In the viability testing from the plates exposed to silver solution (370 mg/ml) no re-growth occurred as compared to the control plates exposed to silver nitrate solution.

USE - For the treatment of bacterial condition, microbial condition, inflammatory condition, fungal condition, viral condition, autoimmune condition, idiopathic condition, noncancerous growth, cancerous condition, skin condition, or integument condition (e.g. burn, eczema, erythroderma, insect bite, mycosis fungoides, pyoderma gangrenosum, eythrema multiforme, rosacea, onychomyocosis, acne, psoriasis, Reiter's syndrome, pityriasis rubra pilaris, hyperpigmentation, vitiligo, hypertropic scarring, keloid, lichen planus, age related skin disorders and hyperproliferative variants of the disorders of keratinization), a respiratory condition (e.g. lupus pneumonitis, asthma, emphysema, bronchitis, pulmonary edema, acute respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary fibrosis, pulmonary atelectasis, tuberculosis, pneumonia, sinusitis, pharyngitis, mucositis, chronic obstructive pulmonary disease, bronchiectasis, and cystic fibrosis), musculo-skeletal condition (e.g. tendonitis, osteomyelitis, fibromyalgia, bursitis and arthritis), a circulatory condition (e.g. arteriosclerosis, septicemia, leukemia, ischemic vascular disease, lymphangitis and atherosclerosis), cancer (e.g. tumors and hematologic malignancies), mucosal conditions and serosal conditions (e.g. pericarditis, Bowen's disease, prostatitis, sinusitis, digestive disorders, toxic epidermal necrolysis syndrome, Stevens Johnson syndrome, cystic fibrosis, bronchitis, pneumonia, pharyngitis, common cold, **ear** infections, sore throat, sexually transmitted diseases, inflammatory bowel disease, colitis, hemorrhoids, thrush, dental conditions, oral conditions, conjunctivitis, and periodontal conditions) (all claimed). In industrial applications to reduce and prevent microbial growth on industrial surfaces e.g. heating pipes and furnace filters, and to prevent spread of microorganisms e.g. heating and air circulation systems within building.

ADVANTAGE - The metal containing materials enhance therapeutic efficacy of the dry powder formulations by forming metastable high levels

of metal hydroxide species, which provide therapeutic properties directly or indirectly; and by releasing cluster of metals. The dry powder formulations can efficiently treat variety of conditions by facilitating access of the metals to remote areas. The method induces apoptosis and modulates **matrix metalloproteinases.**
Dwg.0/9
FS CPI
FA AB; DCN
MC CPI: B05-A03B; B14-A01; B14-A01B1; B14-A02; B14-A03; B14-A04; B14-C01; B14-C03; B14-C09; B14-D07C; B14-E04; B14-E10A; B14-E10C; B14-F01B; B14-F02; B14-F07; B14-G02D; B14-H01; B14-H03; B14-J05; B14-K01; B14-N01; **B14-N02**; B14-N03; B14-N04; B14-N05; B14-N06; B14-N07; B14-N16; B14-N17; B14-S06; D08-A; D08-A05; D08-B09A; D09-A01; D09-E
TECH UPTX: 20031128
TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The metal-containing compound is metals or alloys. The metal-containing compound is metal oxides, metal nitrides, metal borides, metal halides and metal hydrides. The metal-containing compound comprises a metal selected from silver, gold, platinum or palladium (preferably silver), an ionic compound, atoms, molecules or clusters, an atomically disordered crystalline compound, or an antimicrobial compound.
Preferred Powder: The free-standing powder has an average particle size of at most two microns.
ABEX UPTX: 20031128
ADMINISTRATION - Administration is by injection with a needle less injector, inhalation with a dry powder inhaler (claimed) to the hyperplastic tissue, tumor tissue or cancerous lesion. Administration is also by oral, topical route or in the form of a dressing.

EXAMPLE - No relevant example given.

L151 ANSWER 13 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-247939 [24] WPIX
DNC C2003-063803
TI Composition useful for removing human cerumen from the external **ear** canal comprises bicarbonate or enzyme and an aqueous vehicle comprising a demulcent and a surfactant.
DC A96 B04 D16 D21 E19
IN CAGLE, G D; OWEN, G R; RIDRUEJO, N J; WALL, G M
PA (ALCO-N) ALCON INC; (CAGL-I) CAGLE G D; (OWEN-I) OWEN G R; (RIDR-I) RIDRUEJO N J; (WALL-I) WALL G M
CYC 34
PI WO 2003003976 A2 20030116 (200324)* EN 29 A61K000-00
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
W: AU BR CA CN JP KR MX NO NZ PH PL SG US ZA
EP 1337228 A2 20030827 (200357) EN A61K007-00
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
NO 2004000005 A 20040102 (200416) A61K000-00
BR 2002010493 A 20040622 (200442) A61K038-43
KR 2004018416 A 20040303 (200443) A61K033-10
US 2004126436 A1 20040701 (200444) A61K033-00
AU 2002345778 A1 20030121 (200452) A61K000-00
MX 2003010881 A1 20040201 (200473) A61K033-10
ADT WO 2003003976 A2 WO 2002-US19756 20020621; EP 1337228 A2 EP 2002-744528 20020621, WO 2002-US19756 20020621; NO 2004000005 A WO 2002-US19756 20020621, NO 2004-5 20040102; BR 2002010493 A BR 2002-10493 20020621, WO 2002-US19756 20020621; KR 2004018416 A KR 2003-717312 20031231; US 2004126436 A1 Provisional US 2001-302959P 20010703, Cont of WO 2002-US19756 20020621, US 2003-705441 20031110; AU 2002345778 A1 AU

2002-345778 20020621; MX 2003010881 A1 WO 2002-US19756 20020621, MX 2003-10881 20031127

FDT EP 1337228 A2 Based on WO 2003003976; BR 2002010493 A Based on WO 2003003976; AU 2002345778 A1 Based on WO 2003003976; MX 2003010881 A1 Based on WO 2003003976

PRAI US 2001-302959P 20010703; US 2003-705441 20031110

IC ICM A61K000-00; A61K007-00; A61K033-00; A61K033-10; A61K038-43
ICS A61K033-10

AB WO2003003976 A UPAB: 20030410
NOVELTY - A composition comprises bicarbonate or an enzyme and an aqueous vehicle comprising a demulcent and a surfactant.
ACTIVITY - Auditory.
MECHANISM OF ACTION - None given.
USE - For removing human cerumen from the external **ear** canal (claimed). Also useful for treating otic and nasal conditions; and cleansing the middle or external **ear** of the viscous exudate (e.g. **otitis** media, mucoid **otitis** media, serous **otitis** media or chronic **otitis** media).
ADVANTAGE - The composition exhibits superior stability and is more viable and safe. The composition maintains a stable pH of 40 deg. C for three months after the preparation.
Dwg.0/10

FS CPI

FA AB; DCN

MC CPI: A12-V01; B04-C02A1; B04-C03A; B04-C03B; B04-C03D; B04-L05; B05-C04; B10-A17; B10-A22; B10-E04C; B12-M06; **B14-N02**; B14-N04; D05-C03; D05-H17A3; D08-B13; E10-A17B; E10-A22A; E10-E04H; E33-D

TECH UPTX: 20030410
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The composition further comprises a preservative, buffer and an enzyme stabilizing agent. The composition is packaged in a bottle within an aluminum foil.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - The demulcent is povidone, glycerin, or propylene glycol, derivatives (preferably glycerin (0.5 - 15 wt/vol.%)). The buffer is citrate. The preservative is benzalkonium halide, alexidine salt, chlorhexidine salt, hexamethylene biguanimide or its polymers (preferably hexamethylene biguanidine). The surfactant is Tetronic 1304 (0.05 - 1 wt/vol.%).

TECHNOLOGY FOCUS - POLYMERS - The demulcent is polyvinyl alcohol, polyethlene glycol or cellulose. The surfactant is polysorbate, 4-(1,1,3,3-tetramethylbutyl)phenol/poly(oxyethylene)polymer, poly(oxyethylene)-poly(oxypropylene)block copolymer, polyethylene glycol ester of fatty acid or 12-18C polyoxypropylene ether of higher alkane (preferably poly(oxyethylene)-poly(oxypropylene)block copolymer). The preservative is poly(dimethylimino-2-butene-1,4-diyl)chloride-alpha-(4-tris(2-hydroxyethyl)ammonium)dichloride. The enzyme stabilizing agent is monomeric or polymeric polyol.
TECHNOLOGY FOCUS - BIOLOGY - The enzyme is a lipase, protease and/or amylase, proteolytic enzyme (preferably pancreatin, trypsin, subtilisin, collagenase, keratinase, carboxypeptidase, papain, bromelain, aminopeptidase, elastase, Aspergillo peptidase, S. griseus (pronase E) and/or dispase (Bacillus polymyxa), microbially derived enzyme, or alkyl trypsin (preferably methyl trypsin (50 - 500 AU/ml)).

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - The bicarbonate is sodium bicarbonate (0.5 - 15 wt/vol.%). The buffer is phosphate, borate, Tris and/or their salts. The enzyme stabilizing agent is calcium ions or borate/boric acid.

ABEX UPTX: 20030410
EXAMPLE - The composition comprising (wt/volume%): sodium bicarbonate (5), sodium citrate.2H2O (3), glycerin (7), Tetronic 1304 (0.25), benzalkonium chloride (0.01), and water (balance) was prepared. The composition showed an absorbency at 2 hours for human 280 nm cerumen of 1659 units/gm/ml.

L151 ANSWER 14 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-239119 [23] WPIX
DNC C2003-061222
TI New N-formyl hydroxylamine compounds useful for treatment of bacterial infection.
DC B03
IN GERCIA, A S; JACOBS, J; JAIN, R K; PATEL, D V; YUAN, Z; GARCIA ALVAREZ, S; GARCIA, A S; ALVAREZ, S G; BROWN, R B; MCCORQUODALE, M S
PA (VICU-N) VICURON PHARM INC; (ALVA-I) ALVAREZ S G; (JACO-I) JACOBS J; (JAIN-I) JAIN R K; (PATE-I) PATEL D V; (YUAN-I) YUAN Z; (BROW-I) BROWN R B; (MCCO-I) MCCORQUODALE M S; (NOVS) NOVARTIS AG; (VERS-N) VERSICOR INC
CYC 88
PI WO 2002102790 A1 20021227 (200323)* EN 35 C07D401-12
RW: AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE TR
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LT LU LV MA MD MK MN MX NO NZ OM PH PL PT RO RU SE SG SI SK TJ TM TN TR TT UA US UZ VN YU ZA ZW
US 2003045479 A1 20030306 (200324) A61K038-05
US 2003210101 A1 20031113 (200382) H03L007-04
EP 1401828 A1 20040331 (200424) EN C07D401-12
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
CZ 2003003388 A3 20040317 (200430) C07D401-12
KR 2004010721 A 20040131 (200436) C07D401-12
SK 2003001524 A3 20040707 (200447) C07D401-12
AU 2002321062 A1 20030102 (200452) C07D401-12
HU 2004000208 A2 20040628 (200452) C07D401-12
BR 2002010377 A 20040810 (200455) C07D401-12
CN 1511152 A 20040707 (200467) C07D401-12
ZA 2003008379 A 20040929 (200468) 72 A61K000-00
JP 2005502606 W 20050127 (200510) 126 C07D207-16
IN 2003001963 P4 20041211 (200530) EN C07D401-12
ADT WO 2002102790 A1 WO 2002-EP6604 20020614; US 2003045479 A1 Provisional US 2001-298419P 20010615, Provisional US 2002-360313P 20020227, US 2002-171706 20020614; US 2003210101 A1 Provisional US 2002-360313P 20020227, US 2003-374446 20030226; EP 1401828 A1 EP 2002-754681 20020614, WO 2002-EP6604 20020614; CZ 2003003388 A3 WO 2002-EP6604 20020614, CZ 2003-3388 20020614; KR 2004010721 A KR 2003-716435 20031215; SK 2003001524 A3 WO 2002-EP6604 20020614, SK 2003-1524 20020614; AU 2002321062 A1 AU 2002-321062 20020614; HU 2004000208 A2 WO 2002-EP6604 20020614, HU 2004-208 20020614; BR 2002010377 A BR 2002-10377 20020614, WO 2002-EP6604 20020614; CN 1511152 A CN 2002-810596 20020614; ZA 2003008379 A ZA 2003-8379 20031028; JP 2005502606 W WO 2002-EP6604 20020614, JP 2003-506263 20020614; IN 2003001963 P4 WO 2002-EP6604 20020614, IN 2003-CN1963 20031210
FDT EP 1401828 A1 Based on WO 2002102790; CZ 2003003388 A3 Based on WO 2002102790; SK 2003001524 A3 Based on WO 2002102790; AU 2002321062 A1 Based on WO 2002102790; HU 2004000208 A2 Based on WO 2002102790; BR 2002010377 A Based on WO 2002102790; JP 2005502606 W Based on WO 2002102790
PRAI US 2002-360313P 20020227; US 2001-298419P 20010615; US 2002-171706 20020614; US 2003-374446 20030226
IC ICM A61K000-00; A61K038-05; C07D207-16; C07D401-12; H03L007-04

ICS A61K031-401; A61K031-4025; A61K031-4402; A61K031-4427; A61K031-4439; A61K031-455; A61K031-4709; A61K031-4725; A61P031-00; A61P031-04; A61P043-00; C07D403-12; C07D405-12; C07K005-04; C12N001-00; C12N005-00

AB WO2002102790 A UPAB: 20030407

NOVELTY - N-Formyl hydroxylamine compounds, their salts or prodrug are new.

DETAILED DESCRIPTION - N-Formyl hydroxylamine compounds of formula (I), their salts or prodrug are new.

X = -CH2-, -S-, -CH(OH)-, -CH(OR)-, -CH(SH)-, -CH(SR)-, -CF2-, -C=N(OR- or -CH(F)-;

R = alkyl;

R1 = aryl or heteroaryl;

R2 - R5 = H, or alkyl;

R2 + R4, R2 + R5, R3 + R4 and R3 + R5 = 4-7C cycloalkyl;

n = 0-3.

Provided that when n is 0 then X is -CH2-.

An INDEPENDENT CLAIM is included for preparation of (I).

ACTIVITY - Antibacterial; Antiarteriosclerotic; Antiarthritic; Immunosuppressive; Ophthalmological; Periodontal; Vulnerary; Virucide; Gastrointestinal-Gen.; CNS-Gen.; Dermatological; Gynecological.

MECHANISM OF ACTION - Peptidyl deformylase (PDF) inhibitor.

The antibacterial properties of compound (I) were demonstrated for their ability to inhibitor of PDF selectively. The IC50 of the compounds against **MMP**-7 (**matrix metalloproteinases**) was 10-100 micro M. No results for specific compounds are given.

USE - For treating and/or preventing an infectious disorder, preventing bacterial contamination of a cell culture medium (claimed), particularly infectious disorders, caused by bacterial and prokaryotic organisms, microbial infections, including central nervous system infection, external **ear** infection, infection of the **middle ear** (e.g. acute **otitis** media), infections of the cranial sinuses, eye infections, infections of oral cavity (e.g. infection of teeth, gums and mucosa), upper and lower respiratory tract infection, genitourinary infection, gastrointestinal infection, gynecological infection, septicemia, bone and joint infection, skin and skin structure infection, bacterial endocarditis, burns, antibacterial propylaxis of surgery, antibacterial prophylaxis in immunosuppressed patients (e.g. patient receiving cancer chemotherapy, organ transplant patients) and chronic disease caused by infectious organisms e.g. arteriosclerosis.

ADVANTAGE - The compounds exhibit oral bioavailability greater than 70% and superior selectivity for PDF over **matrix metalloproteinases**-7 (**MMP**-7) (matrilysin).

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B07-D03; B07-F01; B14-A01; B14-F06; B14-N01; **B14-N02**; B14-N03; B14-N05; B14-N07; B14-N17

TECH UPTX: 20030407

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) involves reacting a compound of formula (II) with a compound of formula (III) to obtain (I) in free form which may be converted into salt form or vice versa.

Y = protecting group;

X' = NH or O.

ABEX UPTX: 20030407

ADMINISTRATION - The dosage of (I) is 0.015-50 (preferably 5-20) mg/kg/day and administered locally, systemically, orally, topically, parenterally, subdermally, by inhalation.

EXAMPLE - To a solution of 2-((benzyloxy-formyl-amino)-methyl)-hexanoic acid (1 equivalent (eq)) in dry dioxane (4 ml) at room temperature under nitrogen was added successively Hunig's base (3.3 eq), pyrrolidine-2-carboxylic acid pyridin-2-ylamide (1.1 eq) and O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate HATU (1.1 eq). The mixture was stirred at room temperature for 22 hours. The mixture was partitioned between ethyl acetate and 10% citric acid. The organic layer was washed with brine and saturated NaHCO3, dried over anhydrous Na2SO4, filtered and concentrated. The residue was purified by flash chromatography to give the 1-(2-R-((formyl-hydroxy-amino)-methyl)-hexanoyl)-pyrrolidine-2-S-carboxylic acid pyridin-2-ylamide.

DEFINITIONS - Preferred Definitions:
X = -CH2-;
R2- R4 = H;
R5 = n-butyl;
n = 1;
R1 = 2-pyridyl (substituted on 4-position by ethyl or methyl) or 2-pyridyl N-oxide (substituted on 5-position by fluoro or trifluoromethyl).

L151 ANSWER 15 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2002-500631 [53] WPIX
DNC C2002-141847
TI Novel fusion protein useful for inhibiting protease activity associated with a disorder such as emphysema, asthma, comprises a first protease inhibitor comprising **alpha 1-antitrypsin** and a second protease inhibitor.
DC B04 D16
IN BARR, P J; GIBSON, H; PEMBERTON, P; GIBSON, H L
PA (ARRI-N) ARRIVA PHARM INC; (BARR-I) BARR P J; (GIBS-I) GIBSON H; (PEMB-I) PEMBERTON P
CYC 101
PI WO 2002050287 A2 20020627 (200253)* EN 134 C12N015-62
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
AU 2002041661 A 20020701 (200264) C12N015-62
US 2003073217 A1 20030417 (200329) C12N009-99
EP 1366175 A2 20031203 (200380) EN C12N015-62
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2004537970 W 20041224 (200502) 219 C12N015-09
ADT WO 2002050287 A2 WO 2001-US49256 20011218; AU 2002041661 A AU 2002-41661 20011218; US 2003073217 A1 Provisional US 2000-256699P 20001218, Provisional US 2001-331966P 20011120, US 2001-25514 20011218; EP 1366175 A2 EP 2001-988344 20011218, WO 2001-US49256 20011218; JP 2004537970 W WO 2001-US49256 20011218, JP 2002-552164 20011218
FDT AU 2002041661 A Based on WO 2002050287; EP 1366175 A2 Based on WO 2002050287; JP 2004537970 W Based on WO 2002050287
PRAI US 2001-331966P 20011120; US 2000-256699P 20001218;
US 2001-25514 20011218
IC ICM C12N009-99; C12N015-09; C12N015-62
ICS A61K038-55; A61K038-57; A61P011-00; A61P011-06; A61P019-04; **A61P027-16**; A61P031-18; A61P043-00; C07H021-04; C07K014-47;

C07K014-81; C07K019-00; C12N001-15; C12N001-19; C12N001-21; C12N005-06; C12N005-10; C12N015-15; C12P021-02; C12P021-04

AB WO 200250287 A UPAB: 20021031
NOVELTY - A fusion protein (I) comprising a first protease inhibitor comprising an **alpha 1-antitrypsin** or its functionally active portion, and a second protease inhibitor or its functionally active protein, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a polynucleotide (II) encoding (I);

(2) an expression vector (III) comprising (II);

(3) a host cell (IV) comprising (III);

(4) a pharmaceutical composition (V) comprising (I) admixed with a pharmaceutically acceptable vehicle; and

(5) production of (I).

ACTIVITY - Antiasthmatic; auditory; anti-HIV. dermatological; antiinflammatory; antiallergic; antipsoriatic; virucide; vulnerary; antibacterial; immunosuppressive; antirheumatic; antiarthritic; antitumor; antiulcer; osteopathic; cytostatic; nephrotropic; protozoacide; nootropic; neuroprotective; hypotensive.

MECHANISM OF ACTION - Inhibitor of protease activity (claimed); gene therapy.

Experimental protocol is given, but no results are given.

USE - (I) Is useful for inhibiting protease activity associated with a disorder such as emphysema, asthma, chronic obstructive pulmonary disease, cystic fibrosis, **otitis** media, **otitis** external or HIV infection, or for treating an individual suffering from or at risk for a disease or disorder involving unwanted protease activity (claimed).

(I) is useful for treating dermatological diseases such as atopic dermatitis, eczema and psoriasis, in inflammatory responses to viral infection, and for treating herpes infection, corneal or epidermal ulceration, chronic non-healing wounds, sepsis, rheumatoid arthritis, periodontal disease, tumor metastasis and tumor angiogenesis, gastric ulceration, osteoporosis, Paget's disease, glomerulonephritis, scleroderma, malaria, bacterial infection, Alzheimer's disease, hypertension and muscular dystrophy. (II) is useful in gene therapy.

Dwg.0/6

FS CPI

FA AB; DCN

MC CPI: B04-C01G; B04-E02H; B04-E03H; B04-E08; B04-F0100E; B04-L05C; B04-M01; B04-M0100E; B04-N04A0E; B11-A02; B12-M05; B14-A01; B14-A02; B14-A02B1; B14-A03; B14-C03; B14-C06; B14-C09; B14-D07; B14-E08; B14-F02B; B14-G02; B14-G02A; B14-H01; B14-J01; B14-K01A; B14-N01; **B14-N02**; B14-N10; B14-N17; B14-N17B; B14-N17C; B14-S03A; D05-A02C; D05-C12; D05-H08; D05-H12C; D05-H12E; D05-H14; D05-H17C; D05-H18

TECH UPTX: 20020820
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: (I) Is prepared by culturing (IV) under conditions appropriate for expressing (I) and purifying (I) (claimed).

Preferred Protein: In (I), the second protease inhibitor is secretory leukocyte protease inhibitor or a tissue inhibitor of metalloproteases, preferably TIMP-1. The second protease inhibitor inhibits serine protease, metalloprotease, aspartyl protease or cysteine protease. (I) comprises amino acids from about 1-394 of **alpha 1-antitrypsin**, and amino acids from about 1-107 of secretory leukocyte protease inhibitor. The carboxy terminus of amino acids from 1-394 of **alpha 1-antitrypsin** is linked to the amino terminus of amino acids from 1-107 of secretory leukocyte

protease inhibitor or the carboxy terminus of amino acids from 1-107 of secretory leukocyte protease inhibitor is linked to the amino terminus of amino acids from 1-394 of **alpha 1-antitrypsin**
. (I) comprises from about amino acids 1-394 of **alpha 1**
-antitrypsin, and amino acids from about 1-184, preferably 1-126 of tissue inhibitor of metalloproteases-1. The carboxy terminus of amino acids from 1-394 of **alpha 1-antitrypsin** is
linked to the amino terminus of amino acids from 1-184, preferably 1-126 of tissue inhibitor of metalloproteases-1 or the carboxy terminus of amino acids from 1-184, preferably 1-126 of tissue inhibitor of metalloproteases-1 is linked to the amino terminus of amino acids from 1-394 of **alpha 1-antitrypsin.** (I) comprises
from about amino acids 1-394 of **alpha 1-**
antitrypsin and amino acids 1-127 of tissue inhibitor of metalloproteases-1, where the **alpha 1-**
antitrypsin is covalently linked to the tissue inhibitor of metalloproteases-1 through a disulfide bound between amino acid 127 of the tissue inhibitor of metalloproteases-1 and a free cysteine residue of the **alpha 1-antitrypsin.** The free cysteine residue
of the alpha-**antitrypsin** polypeptide is at a position 232 in a sequence comprising 394 amino acids fully defined in the specification.

ABEX UPTX: 20020820

WIDER DISCLOSURE - Also disclosed are:
(1) a kit comprising (I); and
(2) a method of producing (V).

ADMINISTRATION - (I) Is administered by intravenous, topical, subcutaneous, intramuscular, intra-articular, oral or intraocular route or by inhalation.
No dosage details are given.
EXAMPLE - Construction of secretory leukocyte protease inhibitor (SLPI)/ **alpha 1-antitrypsin** (AAT) and tissue inhibitor
of metalloproteases-1 (TIMP-1)/AAT fusion proteins was as follows.
A fusion protein comprising amino acids 1-107 of human SLPI fused to amino acids 1-394 of human AAT was constructed and referred to as SLAPI. The nucleotide sequence which was used in the construction of the SLAPI fusion protein had 1525 base pairs fully defined in the specification. A fusion protein comprising amino acids 1-184 of human TIMP-1 fused to amino acids 1-394 of human AAT was constructed and referred to as TAPI. The nucleotide sequence which was used in the construction of the TAPI fusion protein had 1756 base pairs fully defined in the specification. Expression vectors were constructed as follows. pHG42, a vector for assembling the expression cassette for yeast expression was cloned by sequentially adding polymerase chain reaction (PCR) cloned fragments of the Saccharomyces cerevisiae ADH2 promoter and terminator and the URA3 gene into pBluescript.
Briefly, the ADH2 promoter was amplified with 5'-Xho and BamH1 sites, a 3'-Xba1 site and cloned into pBlsc cut with Xho1/Xba1. The ADH2 terminator was amplified with 5'-Xba1 and Sal1 sites, a 3'-Not1 site and cloned into the ADH2 promoter-containing pBlsc vector Xba1/Not1 to create pHG40. The URA3 gene was amplified with 5'-BamH1 and 3'-Xho1 sites, cloned into pHG40 to generate pHG42. Genes to be expressed were cloned into the Xba1/Sal1 sites 5'- to 3'- and the entire cassette was removed as a Not1/Xho1 fragment for ligation into yeast expression vectors. pHG62 was a yeast expression vector containing the entire S. cerevisiae 2 micron sequence cloned into pBlsc. The B form of 2 micron DNA was amplified by PCR from S. cerevisiae DNA in 2 fragments as Not1/EcoR1 and EcoR1/Xho1 fragments using the unique EcoR1 site of 2 micron DNA.
The entire 2 micron DNA vector was excised Not1/Xho1 for ligation and transformation yeast. Coding sequences for the fusion proteins were constructed. Coding sequences for the fusion proteins were constructed. A

synthetic SLPI gene was chemically synthesized with yeast-preferred codons coding for the mature peptide, amino acids 1-107 and cloned into pUC19. PCR primers were designed with a 5'-Xbal site and a 3'-Nco1 site to subclone SLPI as a fusion with AATyc2. A synthetic AAT gene (AATyc2) was chemically synthesized with yeast-preferred codons that encoded a methionine residue, and amino acids 1-394 of mature AAT, and cloned into pCR4TOPO. A three fragment ligation was assembled with pHG42 Xba1/Sal1 vector, DNA encoding AATyc2 as a NcoI/Sal fragment and cloned into Escherichia coli to create MetSLPI/MetAATyc2 pHG42. The Not1/Xho1 fragment of MetSLPI/MetAATyc2 pHG42 was cloned into pHG62 Not1/Xho1, pKC64 Not1/Xho1, or pKC65 Not1/Xho1. Other expression vectors which were used in the construction of SLAPI and other protease inhibitors were pKC64 and pKC 65, which were modified versions of pHG62 with the yeast LEU2 gene inserted at the novel Pst site of 2 micron DNA.

L151 ANSWER 16 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2001-367273 [38] WPIX
DNC C2001-112564
TI Bioadhesive pharmaceutical composition for treating mucosal epithelial ulceration and/or erosions comprises bioadhesive substance, active substance having **matrix metalloproteinases** inhibitory activity and vehicle.
DC A96 B05 C03
IN GIZURARSON, S; HOLBROOK, W P; KRISTMUNDSDOTTIR, T; SKULASON, S
PA (LIFH-N) LIF-HLAUP EHF BIO-GELS PHARM INC
CYC 95
PI WO 2001028515 A1 20010426 (200138)* EN 52 A61K009-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000078164 A 20010430 (200148) A61K009-00
EP 1267826 A1 20030102 (200310) EN A61K009-00
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2003512310 W 20030402 (200325) 42 A61K045-00
AU 778498 B2 20041209 (200508) A61K009-00
ADT WO 2001028515 A1 WO 2000-IS13 20001022; AU 2000078164 A AU 2000-78164 20001022; EP 1267826 A1 EP 2000-968217 20001022, WO 2000-IS13 20001022; JP 2003512310 W WO 2000-IS13 20001022, JP 2001-531110 20001022; AU 778498 B2 AU 2000-78164 20001022
FDT AU 2000078164 A Based on WO 2001028515; EP 1267826 A1 Based on WO 2001028515; JP 2003512310 W Based on WO 2001028515; AU 778498 B2 Previous Publ. AU 2000078164, Based on WO 2001028515
PRAI IS 1999-5228 19991022
IC ICM A61K009-00; A61K045-00
ICS A61K009-02; A61K009-06; A61K009-08; A61K009-10; A61K009-12; A61K009-127; A61K009-48; A61K009-70; A61K031-00; A61K031-085; A61K031-135; A61K031-14; A61K031-167; A61K031-235; A61K031-245; A61K031-327; A61K031-352; A61K031-4418; A61K031-4704; A61K031-5375; A61K031-60; A61K031-65; A61K033-22; A61K033-30; A61K035-60; A61K035-72; A61K035-78; A61K047-00; A61K047-30; A61K047-32; **A61K047-34**; A61K047-36; A61K047-38; A61K047-42; A61K047-46; A61P001-00; A61P001-02; A61P001-04; A61P011-00; A61P015-00; A61P015-02; A61P027-16; A61P029-00; A61P043-00
AB WO 200128515 A UPAB: 20010711
NOVELTY - A bioadhesive pharmaceutical composition for treating mucosal epithelial ulceration and/or erosions comprises a bioadhesive substance, a

biologically active substance having **matrix metalloproteinases** inhibitory activity and an optional vehicle. The bioadhesive substance and the vehicle release the active substance into the epithelia of the mucosa without affecting its normal flora.

ACTIVITY - Antiulcer; gastrointestinal; gynecological; uropathic; cytostatic; antibacterial; virucide.

MECHANISM OF ACTION - **Metalloproteinase** inhibitor.

USE - The composition is useful for the manufacture of a medicament for the treatment of mucosal epithelial ulceration and/or erosion. The mammal is horse, cow, cat, dog, hamster, guinea pig or other pets or animals for breeding. The formulation is also useful in the treatment of primary herpes simplex, recurrent herpes, coxsackie virus infections in oral or other mucosal surfaces etc.

ADVANTAGE - The formulation does not affect the normal flora or the mucosa and reduces the risk of side effects

Dwg.0/3

FS CPI

FA AB; DCN

MC CPI: A12-V01; B04-B01C1; B04-B01C2; B04-C02; B04-C03; B04-F02; B05-A03A; B05-B02C; B05-C08; B06-A01; B06-A02; B06-D13; B06-F05; B07-A02; B07-E03; B10-A04; B10-A13D; B10-A22; B10-B02A; B10-B02F; B10-B02G; B10-B03B; B10-C03; B10-E02; B12-M01A; B12-M02B; B12-M03; B12-M07; B12-M08; B12-M10A; B12-M11C; B12-M11F; B14-C07; B14-D07C; B14-L09; B14-N17B; B14-R03; B14-S12; C04-B01C1; C04-B01C2; C04-C02; C04-C03; C04-F02; C05-A03A; C05-B02C; C05-C08; C06-A01; C06-A02; C06-D13; C06-F05; C07-A02; C07-E03; C10-A04; C10-A13D; C10-A22; C10-B02A; C10-B02F; C10-B02G; C10-B03B; C10-C03; C10-E02; C12-M01A; C12-M02B; C12-M03; C12-M07; C12-M08; C12-M10A; C12-M11C; C12-M11F; C14-C07; C14-D07C; C14-L09; C14-N17B; C14-R03; C14-S12

TECH UPTX: 20010711

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The active substance is released in a profile comprising release of 10% within at least 10 minutes and at least 20% within at least 30 minutes. The active substance is contained in a concentration of 0.05-0.5 (especially 0.1-0.3) wt% of the composition and the bioadhesive substance in an amount of 0.05-10 (especially 0.1-5) wt% of the composition. The composition is in the form of a hydrogel, gel, film, cream, ointment, lotion, liniment, liposome, solution, suspension, foam, stick, spray, paste, patch, plaster, suppository or gelatin capsule (especially hydrogel or gel with bioadhesive properties to mucosal membranes). The composition also comprises bioadhesive component(s) (selected from more than 20 specified): bioadhesive/water gelling agents such as carbopol 934, carbopol 940, carbopol 941, carbopol 971, carbopol 974, carbopol 980, carbopol 981, carbopol 1342, carbopol 1382, carboxymethylcellulose and hydroxypropylmethylcellulose or their salts, xanthan gums, and/or polycarbophil. The biologically active substance is in dissolved or in particulate form and is selected from tetracyclines or their derivatives such as tetracycline, doxycycline, minocycline or oxytetracycline and in a concentration below antimicrobial concentration. The composition also comprises additional active compound selected from (30 specified): anesthetics such as benzocaine, mepiracaine, astringents such as calamine, zinc oxide, wound cleansers such as benzalkonium chloride, tannic acid, wound healing agents such as fish oils, shark, liver oil and antihistamines such as promethazine and azatadine. The composition further comprises additional ingredients selected from (16 specified) surfactants, organic solvents, pH controlling agents, propellents and/or water.

ABEX UPTX: 20010711

ADMINISTRATION - The composition is administered to a surface of the mucosa including parts which are inflamed, ulcerated, surface eroded wholly or partially extending through the surface of the epithelial layer

but only extending just into the underlying lamina propria. The mucosal surface is selected from surfaces of nose, lungs, mouth, eye, **ear** , gastrointestinal tract, genital tract, vagina and rectum. The active substance is applied in a volume of 0.01-0.5 ml for oral, nasal and ocular mucosa and in a volume not exceeding 30 ml for rectal or vaginal mucosa. The formulation is administered to splenectomized subjects, subjects with cancer or using anticancer drugs or antibiotics, anti-inflammatories, subjects subject to hyper/hypothyroidism or having problems with malabsorption such as diarrhea.

EXAMPLE - Inhibitory activity of doxycycline against metalloproteinases was evaluated using Zymography method (Mackay et al., Cancer Res., 50(18), 5997-6001, 1990). Complete inhibition of metalloproteinase 2 was obtained with 100 microM (48 microg/ml) concentration and 50 microM (24 microg/mol) against metalloproteinase 9.

L151 ANSWER 17 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2001-167802 [17] WPIX
DNC C2001-049999
TI Treatment of eye and **ear** infections prevent tissue destruction by parasitic or microbial infestation by administering protease inhibitor e.g. secretory leucocyte protease inhibitor.
DC B04
IN LEZDEY, D; LEZDEY, J
PA (JDSC-N) J & D SCI INC
CYC 1
PI US 6174859 B1 20010116 (200117)* 4 A61K038-00
ADT US 6174859 B1 US 1999-286740 19990406
PRAI US 1999-286740 19990406
IC ICM A61K038-00
AB US 6174859 B UPAB: 20010328
NOVELTY - Treatment of optic and otic infections, inflammation and kallikrein activity caused by parasites and microbes comprises administration of protease inhibitor comprising **alpha -1 antitrypsin** (AAT), secretory leukocyte protease inhibitor (SLPI) and/or antiplasmin inhibitor, in a carrier, at the site of infection.

An INDEPENDENT CLAIM is included for a composition comprising 0-20 mg/ml of protease inhibitor, 0-1.5 weight% of steroidal antiphlogistic, 0-5 weight% of non-steroidal antiphlogistic and 0-1.5 weight% of hyaluronic acid, in an aqueous carrier base.

ACTIVITY - Antiinflammatory; antiparasitic; antimicrobial; ophthalmological; auditory.

MECHANISM OF ACTION - Protease inhibitor.

USE - Used for treating eye and **ear** infections, which can lead to irreversible damage and loss of sight or hearing, particularly infections due to Pseudomonas, and the protozoan parasites Cryptosporidium parvum and Schistosoma mansoni, which are usually water borne.

ADVANTAGE - The combination of protease inhibitors with the other ingredients is synergistic, so that both antibiotics and antiphlogistics may be used in smaller doses. The therapeutic effect is higher and treatment time shorter.

Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-C02A2; B04-N02; B14-B02; B14-N03; B14-N04; B14-S09
TECH UPTX: 20010328
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred components: The method includes using a steroid, preferably dexamethasone, betamethasone or triamcinolone acetonide, antibiotics, preferably active against

Pseudomonas; bradykinin antagonists and hyaluronic acid to promote healing, particularly of corneal injury.

ABEX UPTX: 20010328

ADMINISTRATION - Administration is as an ointment or as liquid drops in buffer or physiological saline.

EXAMPLE - A mixture of **alpha-1 antitrypsin** (5 mg), hydroxypropyl methylcellulose (2.5 g) and ionically balanced pH 7.4 phosphate buffer to make to 100 g was prepared. Drops were dosed into the infected **ear** of a patient suffering from swimmer's **ear** three times a day. Pain was reduced with the initial dose.

L151 ANSWER 18 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2000-611339 [58] WPIX
CR 2000-572151 [50]; 2000-587294 [50]; 2000-594139 [50]
DNC C2000-182850
TI Treating herpes virus infection and associated disease by administering alpha1-antitrypsin or compound with similar activity.
DC B05 C03 D16
IN SHAPIRO, L
PA (UYTE-N) UNIV TECHNOLOGY CORP
CYC 87
PI WO 2000051625 A1 20000908 (200058)* EN 86 A61K038-08
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000038640 A 20000921 (200065) A61K038-08
ADT WO 2000051625 A1 WO 2000-US5557 20000303; AU 2000038640 A AU 2000-38640 20000303
FDT AU 2000038640 A Based on WO 2000051625
PRAI US 1999-153942P 19990915; US 1999-123167P 19990305
IC ICM A61K038-08
ICS A61K038-57; A61P031-22
AB WO 200051625 A UPAB: 20001214
NOVELTY - Treating herpes virus (HV) infection and associated disease comprises administering an agent (I) with mammalian **alpha 1-antitrypsin** (aaT) or aaT-like activity.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a pharmaceutical composition comprising a peptide of formula (A) or its salts.

Nt = amino acid (aa), including C, acetyl, succinyl or is absent;
X1 = aa, including F or A;
X2 = aa, including C, V, L, M, I, A, C or S;
X3 = aa, including F, A, V, M, L, I, Y or C;
X4 = aa, including L, A, F, I, V, C, G or S;
X5 = aa, including M, A, I, L, V, F or G;
Ct = aa, including C, an amide or ester, or is absent.
aa Has L- or D-configuration.

ACTIVITY - Antiviral; cytostatic; neuroprotective; antipyretic; dermatological; antiulcer; hepatotropic; antidiarrheal; antibacterial.

Herpes simplex-1 or -2 was used to infect semi-continuous human lung fibroblasts in the presence or absence of aaT, then virus removed and the cells cultured. The amount of virus produced was determined by enzyme-linked immunosorbent assay and the measured optical density was 0.8 in the absence of aaT but only 0.5 when aaT was present at 3 mg/ml.

MECHANISM OF ACTION - Serine protease **inhibitor**; **trypsin inhibitor.**

USE - Used for treating HV infection mediated by an endogenous serine protease or SP-like activity and **inhibiting** the spread or onset of viral infection mediated by endogenous SP or SP-like activity, and for preventing sexually transmitted diseases (all claimed) by intravaginal or intrarectal administration of (I) or its derivatives that can **inhibit** caspase, proteinase-3, cathepsin G and/or elastase. (I) Is used for treating infection by herpes simplex-1 and -2 viruses, cytomegalovirus, Epstein-Barr virus, varicella zoster virus, herpes zoster and human herpes viruses 5, 6 and/or 8. (I) Is used for treating malaise, fever, chills, rhinitis, diarrhea, atopic eczema, encephalitis, keratoconjunctivitis, pharyngitis, gingivostomatitis, hepatitis, recurrent orofacial mucocutaneous lesions or herpes labialis, chicken pox skin sores, erythema multiforme, idiopathic burning mouth, aphthous ulceration, Behcet's syndrome, mononucleosis, Burkitt's lymphoma and other tumors and neuropathies. Particularly, (I) is used against HV infections of the mucosa (oral, **middle ear**, gastrointestinal, urogenital, airway/lung, eye, peritoneal membranes etc.), including sexually transmitted diseases. Treatment with (I) is also used to restore defective levels of functional endogenous aaT and to prevent development of such a condition, in treating infections by viruses other than herpes, to prevent bacterial colonization concurrent with viral infection and also very generally wherever **inhibition** of serine protease activity is required, e.g. in medicine, biology, agriculture or microbial fermentation.

Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: B04-C01A; B07-D13; B07-E04; B07-F03; B10-A08; B10-A10; B10-A17; B14-A01; B14-A02A3; B14-C04; B14-D07C; B14-E02; B14-E08; B14-H01; B14-N03; B14-N04; B14-N06B; B14-N12; B14-N16; B14-N17; C04-C01A; C07-D13; C07-E04; C07-F03; C10-A08; C10-A10; C10-A17; C14-A01; C14-A02A3; C14-C04; C14-D07C; C14-E02; C14-E08; C14-H01; C14-N03; C14-N04; C14-N06B; C14-N12; C14-N16; C14-N17; D05-H17A6; D05-H17B6

TECH UPTX: 20001114

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred materials: (I) Comprises: (i) aaT, particularly isolated from wild-type, mutant or transgenic mammalian sources;
(ii) a peptoid substituted by oxadiazole, thiadiazole or triazole, phenylene dialkanoate, tetrazole, guanidinobenzoic acid, phenylsulfonylamide, sulfide, sulfoxide, sulfone, amidine, amidinophenol or their derivatives, or
(iii) peptides (A).

ABEX UPTX: 20001114

SPECIFIC COMPOUNDS - About 90 compounds are used e.g: (benzyloxycarbonyl)-L-valyl-N-(1-(2-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl)-L-prolinamide (Ia).
27 Peptides (A) are used e.g. Phe-Val-Phe-Leu-Met.

ADMINISTRATION - (I) is administered at 1 mug to 100 mg/kg/day, preferably 10-25 mg/kg/day, systemically or topically. When administered topically, (I) may be combined with an anesthetic, analgesic and/or antibiotic.

L151 ANSWER 19 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 1997-077259 [07] WPIX

CR 2000-205215 [18]

DNC C1997-024781

TI Reversible cysteine protease inhibitors used to treat e.g. arthritis, - and tumour invasion, inflammation and malaria, are new or known N, N'-substd. ethylene di amine derivs..

DC B04 B05 C03

IN KLAUS, J L; KUO, E Y; PALMER, J T; RASNICK, D
PA (AXYS-N) AXYS PHARM INC; (ARRI-N) ARRIS PHARM CORP
CYC 73
PI WO 9640737 A1 19961219 (199707)* EN 83 C07K005-00
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN
AU 9659755 A 19961230 (199716)
ZA 9604751 A 19970326 (199718) 78 C07K000-00
NO 9705742 A 19980205 (199816) C07D295-26
EP 832099 A1 19980401 (199817) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
CZ 9703906 A3 19980415 (199821)
JP 11507045 W 19990622 (199935) 94 C07C311-18
NZ 309560 A 19990828 (199939)
KR 99022395 A 19990325 (200023) C07K005-00
AU 723658 B 20000831 (200046) C07K005-00
TW 438591 A 20010607 (200175) A61K031-535
CN 1192219 A 19980902 (200276) C07K005-00
ADT WO 9640737 A1 WO 1996-US8559 19960603; AU 9659755 A AU 1996-59755 19960603; ZA 9604751 A ZA 1996-4751 19960606; NO 9705742 A WO 1996-US8559 19960603, NO 1997-5742 19971205; EP 832099 A1 EP 1996-917069 19960603, WO 1996-US8559 19960603; CZ 9703906 A3 WO 1996-US8559 19960603, CZ 1997-3906 19960603; JP 11507045 W WO 1996-US8559 19960603, JP 1997-501116 19960603; NZ 309560 A NZ 1996-309560 19960603, WO 1996-US8559 19960603; KR 99022395 A WO 1996-US8559 19960603, KR 1997-708875 19971205; AU 723658 B AU 1996-59755 19960603; TW 438591 A TW 1996-106569 19960601; CN 1192219 A CN 1996-195858 19960603
FDT AU 9659755 A Based on WO 9640737; EP 832099 A1 Based on WO 9640737; CZ 9703906 A3 Based on WO 9640737; JP 11507045 W Based on WO 9640737; NZ 309560 A Based on WO 9640737; KR 99022395 A Based on WO 9640737; AU 723658 B Previous Publ. AU 9659755, Based on WO 9640737
PRAI US 1995-474993 19950607
REP 2.Jnl.Ref; JP 63275575; WO 9418185
IC ICM A61K031-535; C07C311-18; C07D295-26; C07K000-00; C07K005-00
ICS A61K031-18; A61K031-27; A61K031-495; A61K038-04; A61K038-55; C07C311-08; C07C311-15; C07C311-16; C07D295-20; C07D295-215; C07D295-22; C07K005-02
ICI C07M007:00
AB WO 9640737 A UPAB: 20021125
Reversible cysteine **protease** inhibitors (I) with a dissociation constant for inhibition (Ki) of not more than 100 mM comprise two N-substits. R', R'' linked via an opt. substd. ethylene diamine. R', R'' = acyl, alkoxycarbonyl, sulphonyl, sulphamoyl, sulphinyl, carbamoyl, peptidyl, acylpeptidyl, alkoxycarbonylpeptidyl, sulphonylpeptidyl, sulphamoylpeptidyl, sulphinylpeptidyl or carbamoylpeptidyl.

Also claimed are the following. (A) a method of inhibiting a cysteine **protease** inhibitor, by reversibly binding an inhibitor of formula A-NR3-CHR1-CH2-NR4-X (Ia); A, X = R', R''; R1 = H or aminoacid side chain; R3, R4 = H; or R3+R4 = opt. substd. ethylene; (B) a cysteine **protease** inhibited by an inhibitor of formula (Ia); and (C) the detection of cysteine **protease** in a sample by (i) assaying the sample for **protease** activity using a **protease** substrate and (ii) assaying for **protease** activity in the presence of a known concentration of (Ia). Cpds. of formula A1-NR23-CHR21-CH2-NR24-X1 (Ib), and their salts, isomers and mixts. of isomers are new. A1, X1 = independently X1R13 (but not both H); R13 = H, alkoxycarbonylalkanoyl, alkoxycarbonyl, alkanoyl (opt. substd. by carboxy,

alkoxycarbonyl or heterocyclalkylalkanoyl amino), cycloalkylcarbonyl, heterocycloalkylcarbonyl (opt. substd. by OH, alkyl, heterocycloalkyl, alkanoyl, alkyloxycarbonyl, arylalkoxycarbonyl or heterocycloalkylcarbonyl), carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, aralkanoyl, aroyl, alkylsulphonyl, arylsulphonyl, aralkylsulphonyl, alkylsulphamoyl, dialkylsulphamoyl, arylsulphamoyl, alkylsulphinyl, dialkylaminosulphinyl or arylsulphinyl; X1 = bond, -Y-Z-[X3-X4-Z]n-CO- or -Y-Z-[X3-X4-Z]n-CO-NH-CO-; n = 0-9; X3-X4 = -CO-NR14-, -CH2NR14, -COCH2- or -NR14CO; Y = CHR14- or -NR14-; Z = -(CH2)2-, -C(R15)(R16)- or -N(R16)-; R14 = H; R15 = H or Me; R16 = H, alkyl (opt. substd. by OH, alkoxy, amino, alkylamino, dialkylamino, ureido, alkylureido, mercapto, alkylthio, carboxy, carbamoyl (opt. substd. by 1-2 alkyl), alkylsulphinyl, alkylsulphonyl, guanidino, -P(O)(OR12)2, -OP(O)(OR12)2, -OP(O)(R12)2, all opt. protected), cycloalkyl, cycloalkylalkyl, aryl or aralkyl (both opt. ring substd. by 1-3 OH, NH2, guanidino, halo, alkyl, haloalkyl, alkoxy or aryl, all opt protected); or R14+R16 = -CH2CH2CH2-, -(CH2)4 or 1,2-phenylene dimethylene (opt. substd. by OH, protected OH or oxo); R12 = H or alkyl; R21= H, CN, CO2H, alkoxycarbonyl, alkanoyl, carbamoyl, (opt. substd. by 1-2 alkyl), alkoxyalkylcarbamoyl, aminoalkylcarbamoyl, R16 or X2R13; X2 = -Y-Z-[X3-X4-Z]n-CO- or -Y-Z-[X3-X4-Z]n-CO-NH-CO-; R23, R24 = R14; or R3+R4 = opt. substd. ethylene.

USE - (Ia) are useful in treating cysteine-**protease** -associated disorders (claimed), including arthritis, muscular dystrophy, inflammation, tumour invasion, glomerulonephritis, malaria and other parasite-borne infections. (I) are for human or veterinary use. The cpds. are useful in treating periodontal disease such as gingivitis, leishmaniasis, filariasis, osteoporosis, osteoarthritis and especially viral diseases by inhibiting **proteases** necessary for viral replication. The cpds. are useful in disorders involving interleukin-1B converting enzyme (ICE) in the treatment of inflammation and immune- based disorders of the lung, airways, CNS and surrounding membranes, eyes, **ears**, joints, bones, connective tissues, cardiovascular system, gastrointestinal and urogenital systems, the skin and mucosal membranes; including infections such as meningitis and salpingitis, septic shock, reperfusion injury, disseminated intravascular coagulation and/or adult respiratory distress syndrome, acute or chronic inflammation due to antigens, antibodies and/or complement deposition, diabetes mellitus, multiple sclerosis, Alzheimer's disease, cancer metastasis, cholangitis, colitis, encephalitis, endocarditis and pancreatitis. Bone and cartilage reabsorption may be treated along with excessive deposition of extracellular **matrix.** The cpds. may be used in the treatment of tumours that produce IL1 as a growth factor and in preventing cachexia-related tumours. The cpds. may also be used in drug potentiation, involving co-admin. or sequential admin. with a drug which could be inactivated via endogenous proteolysis. (I) may be used as antibacterial agents to prevent tissue damage. (I) may also be used for the removal, identification or inhibition of contaminating cysteine **proteases** in a sample; bound to a chromatographic support to form an affinity chromatography column, for removing cysteine **proteases** or identify new ones; in diagnostic kits used with fluids such as blood or saliva, or in cell cultures (fungi, yeast, bacteria, plant, viral or mammalian). Most of the cpds. are selective inhibitors of cysteine **protease**, and others also inhibit other **proteases** such as serine, aspartyl and other **metalloproteases**, to a lesser extent.

Admin. in the treatment of cysteine-mediated disorders is e.g. oral, subcutaneous, transdermal or intraperitoneal.

ADVANTAGE - The cpds. function reversibly, with tight binding (low Ki values) between inhibitor and target enzyme.

Dwg.0/5
FS CPI
FA AB; DCN
MC CPI: B05-B01P; C05-B01P; B10-A17; C10-A17; B10-B01; C10-B01; B11-C08E3; C11-C08E3; B12-K04A; C12-K04A; B14-A03B; C14-A03B; B14-C03; C14-C03; B14-C09; C14-C09; B14-D07C; C14-D07C; B14-H01B; C14-H01B

L151 ANSWER 20 OF 20 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1996-277462 [28] WPIX
DNC C1996-088005
TI Regulating metallo proteinase activity by adjusting concentration of nitric oxide
- useful for treating tumour metastasis, **otitis** media, pulmonary emphysema, etc..
DC B05
IN MURRELL, G A C; MURRELL, G A
PA (NYRU-N) NEW YORK SOC RUPTURED & CRIPPLED MAINTAI
CYC 20
PI WO 9616648 A1 19960606 (199628)* EN 40 A61K031-20
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP NZ
AU 9642479 A 19960619 (199640) A61K031-20
ADT WO 9616648 A1 WO 1995-US15529 19951121; AU 9642479 A AU 1996-42479 19951121
FDT AU 9642479 A Based on WO 9616648
PRAI US 1994-346146 19941129
REP 1.Jnl.Ref
IC ICM A61K031-20
AB WO 9616648 A UPAB: 19960719
Regulating the activity of **matrix metalloproteinases** in a biological tissue comprises adjusting the concentration of nitric oxide to which the **metalloproteinases** are exposed.

Also claimed are: (A) a method for inhibiting metastasis of malignant tumour cells comprising decreasing the concentration of nitric oxide in the vicinity of the cells; (B) a method for treating **otitis** media comprising admin. of an agent that reduces the concentration of nitric oxide in the **middle ear** sinuses; (C) a method for treating pulmonary emphysema comprising admin. by inhalation of an agent that decreases the local concentration of nitric oxide in the pulmonary tissue; (D) a method for treating scleroderma comprising admin. of an agent that increases the concentration of nitric oxide in the vicinity of skin affected by the scleroderma; and (E) a method for preventing loosening of surgical implants comprising admin. of an agent that decreases the concentration of nitric oxide in the vicinity of the implant.

The concentration of nitric oxide to which the **metalloproteinases** are exposed is pref. decreased by 50-100% below the concentration of nitric oxide that is present in the absence of an agent that decreases the nitric oxide concentration The agent is monomethyl arginine.

USE - The methods can be also used for treating or alleviating diseases of collagen metabolism such as systemic scleroderma, for reducing bone inflammation caused by degeneration of surgical implants and for treating adult respiratory distress syndrome and periodontal disease.
Dwg.0/6
FS CPI
FA AB; DCN
MC CPI: B10-A17; B14-F02D2; B14-H01B; **B14-N02**; B14-N17

```
=> d his

     (FILE 'HOME' ENTERED AT 14:02:58 ON 21 JUN 2005)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 14:03:04 ON 21 JUN 2005
L1             1 S US20040175383/PN OR (US2003-731375# OR WO2003-US39053 OR US20
               E BARR P/AU
L2           259 S E3,E7,E22-30
               E PEMBERTON P/AU
L3            34 S E3,E4,E8,E10
               E ANTONELLI P/AU
L4            12 S E3,E7
               E SCHULTZ G/AU
L5           208 S E3,E13
               E SCHULTZ GREG/AU
L6            94 S E3-E5,E8,E9
               E SUNDIN D/AU
L7            10 S E7,E8
               E ARRIVA/PA,CS
L8             9 S E3-E10
               E U FL/PA,CS
               E U OF FL/PA,CS
               E UN FL/PA,CS
               E UN OF FL/PA,CS
               E UNI FL/PA,CS
               E UNI OF FL/PA,CS
               E UNIV FL/PA,CS
L9            15 S E5-E10
               E UNIV OF FL/PA,CS
L10           59 S E5-E8,E10-E24
L11         4780 S E25-E79
               E UNIVER FL/PA,CS
               E UNIVER OF FL/PA,CS
               E UNIVERS FL/PA,CS
               E UNIVERS OF FL/PA,CS
               E UNIVERSITY FL/PA,CS
L12           56 S E6-E18
               E UNIVERSITY OF FL/PA,CS
L13         1247 S E33-E205
               E FLORIDA/PA,CS
L14        69197 S E3,E4

     FILE 'REGISTRY' ENTERED AT 14:09:55 ON 21 JUN 2005
L15            1 S ILOMASTAT/CN
               E C20H28N4O4/MF
L16           32 S E3 AND NC4-C6/ES AND 2/NR
L17            7 S L16 AND BUTANEDIAMIDE
L18            6 S L17 NOT 200866-76-8
L19            6 S L15,L18
               SEL RN
L20            0 S E1-E6/CRN
L21          674 S (?MATRIX?(L)?METALLO?(L)(?PROTEINASE? OR ?PROTEASE?))/CNS
L22          583 S (?MATRIX?(L)(?METALLOPROTEINASE? OR ?METALLOPROTEASE?))/CNS
               E MMP
L23          790 S E3-E102
L24          674 S L21,L22
L25          349 S L24 AND L23
L26          674 S L24,L25
```

```
L27          441 S L23 NOT L26
                 E ANTITRYPSIN
L28           83 S E3
L29           85 S ANTI TRYPSIN
                 E AAT
L30          452 S E3
                 E SCAN
                 E RAAT
L31            4 S L30 AND L28,L29
L32          141 S ALPHA()1()(ANTITRYPSIN OR ANTI TRYPSIN OR TRYPSIN INHIBIT?)

     FILE 'HCAPLUS' ENTERED AT 14:18:38 ON 21 JUN 2005
L33        20912 S L28-L32
L34         5525 S ALPHA()1()(ANTITRYPSIN OR ANTI TRYPSIN)
L35         5582 S ALPHA()1(L)(ANTITRYPSIN OR ANTI TRYPSIN)
L36         1441 S ALPHA()1(L)TRYPSIN(L)INHIBIT?
L37        22445 S L33-L36
L38        43494 S L26 OR L27
L39        15830 S ?MATRIX?(L)?METALLO?(L)(?PROTEINASE? OR ?PROTEASE?)
L40        15738 S ?MATRIX?(L)(?METALLOPROTEINASE? OR ?METALLOPROTEASE?)
L41           15 S ?MATRIXMETALLO?(L)(?PROTEINASE? OR ?PROTEASE?)
L42           15 S ?MATRIXMETALLOPROTEINASE? OR ?MATRIXMETALLOPROTEASE?
L43        13586 S MMP?
L44        48294 S L38-L43
L45          100 S L19
L46          215 S ILOMASTAT OR CS610 OR CS 610 OR GM6001 OR GM 6001 OR GALARDIN
L47          227 S L45,L46
                 E OTITIS/CT
                 E E3+ALL
L48          471 S E1,E2,E3
                 E OTITI? MEDI?
L49         1294 S OTITI? MEDI?
L50         1656 S E12
                 E TYMPANIC MEMBRANE/CT
                 E E3+ALL
L51          112 S E2
L52          407 S TYMPAN?(L)MEMBRAN?
                 E AUDITORY CANAL/CT
L53          116 S AUDITORY CANAL
                 E MIDDLE EAR
                 E MIDDLE EAR/CT
                 E E3+ALL
L54          439 S E2
                 E TYMPANOSOMY/CT
                 E TYMPANOSTOMY/CT
L55           35 S TYMPANOSTOM?
                 E OTORRHEA/CT
                 E OTORRHEA
L56           37 S E3-E5
                 E EAR/CT
L57         9213 S E3-E63
L58        12277 S E3+OLD,NT,PFT,RT OR E54+OLD,NT,PFT,RT
L59        12960 S L48-L58
L60           23 S L59 AND L37
L61           73 S L59 AND L44
L62            2 S L59 AND L47
L63            4 S L1-L14 AND L60-L62
                 E PEMBERTON P/AU
L64           37 S E3,E4,E9,E10
L65            4 S L64 AND L60-L62
```

```
L66            4 S L63,L65
L67           84 S L60-L62 NOT L66
L68           76 S L67 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L69           19 S L68 AND L37
L70            5 S L69 AND L44
L71            0 S L69 AND L47
L72           19 S L69,L70
                 SEL DN AN 3-5 10-12 15 16
L73            8 S L72 AND E1-E24
L74           57 S L68 NOT L69-L73
                 SEL DN AN 17 37 48 49 L74
L75            4 S E25-E36 AND L74
L76            3 S L75 NOT 3/SC
L77           15 S L66,L73,L76 AND L1-L14,L33-L76
                 SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 14:52:28 ON 21 JUN 2005
L78            6 S E37-E42
L79            1 S L78 AND L19
L80            4 S L78 AND L26,L27
L81            1 S L78 AND L28-L32

     FILE 'REGISTRY' ENTERED AT 14:53:40 ON 21 JUN 2005

     FILE 'HCAPLUS' ENTERED AT 14:54:03 ON 21 JUN 2005

     FILE 'MEDLINE' ENTERED AT 15:10:48 ON 21 JUN 2005
L82           16 S L19
L83          217 S L46
L84          217 S L82,L83
L85         2253 S L28-L32
L86        10309 S L34-L36
L87        12523 S L85,L86
L88         2843 S L26 OR L27
L89        22594 S L39-L43
L90        25406 S L88,L89
                 E ALPHA 1-ANTITRYPSIN/CT
                 E E3+ALL
L91        12523 S E42+NT OR L87
                 E MATRIX METALLOPROTEINASE/CT
                 E E4+ALL
                 E E2+ALL
                 E E26+ALL
L92        53496 S E6+NT OR L90
                 E EAR/CT
L93        59245 S E3+NT
                 E OTITIS/CT
                 E E3+ALL
L94        83145 S E3+NT
L95           47 S L93,L94 AND L91
L96          148 S L93,L94 AND L92
L97            6 S L93,L94 AND L84
L98          176 S L95-L97 AND PY<=2002
L99           44 S L98 NOT AB/FA
L100         132 S L98 NOT L99
L101         112 S L100/ENG
L102          20 S L100 NOT L101
                 SEL DN AN 15 17
L103           2 S L102 AND E1-E4
                 SEL DN AN L101 6 9 23 36 40 46 64 67 68 71 82 96
```

```
L104          12 S L101 AND E5-E28
                 E TYMPANOSTOMY/CT
                 E E3+ALL
                 E E2+ALL
L105        1404 S E8+NT
L106        8396 S E7+NT
L107           1 S L105,L106 AND L84
L108           4 S L105,L106 AND L87
L109           3 S L105,L106 AND L90
L110           8 S L105,L106 AND L91,L92
L111           8 S L107-L110
L112           8 S L111 AND PY<=2002
L113          19 S L103,L104,L112 AND L82-L112

     FILE 'MEDLINE' ENTERED AT 15:31:40 ON 21 JUN 2005

     FILE 'WPIX' ENTERED AT 15:31:52 ON 21 JUN 2005
L114          19 S L46/BIX
                 E ILOMASTAT/DCN
                 E ILOMASTAT/SDCN
                 E ILOMASTAT/CN
L115           1 S E3
                 E RA2BM/DCN
L116          16 S E66-E72
L117          19 S L114,L116
L118         523 S L34/BIX OR L35/BIX OR L36/BIX
                 E ANTITRYPSIN/CN
L119           2 S E4-E6
                 E RA0Y1/DCN
                 E RA0Y1/DCN
L120          13 S E128-E133
                 E RA0AQU/DCN
L121          80 S E3-E13
L122         552 S L118-L121
L123        2318 S L39/BIX OR L40/BIX OR L41/BIX OR L42/BIX OR L43/BIX
                 E MATRIX/CN
L124           9 S E4-E16
L125         196 S (RAAP2X OR RA9NRC OR RA7N1V OR RA6RBL OR RA2UUK OR RA2S0O OR
L126        2422 S L123,L125
L127        1003 S A61P027-16/IPC
L128        4268 S P921/M0,M1,M2,M3,M4,M5,M6
L129        8414 S (B12-L04 OR C12-L04 OR B14-N02 OR C14-N02)/MC
L130           1 S L117 AND L127-L129
L131          21 S L122 AND L127-L129
L132          51 S L126 AND L127-L129
L133           0 S L131 AND L132
L134        5156 S A61K031-56/IPC OR (B04-J02 OR C04-J02)/MC
L135           2 S L131,L132 AND L134
                 E RA0Y1W/DCN
L136          13 S E3-E8
                 E RA0Y1W/SDCN
L137           1 S E3
                 E RA012O/DCN
L138        1369 S E3-E17
                 E RA012O/SDCN
L139           2 S E3
L140         552 S L136 OR L122
L141          21 S L140 AND L127-L129
L142          21 S L131,L141
L143        5158 S L139,L134
```

```
L144          2 S L143 AND L142
L145          2 S L130,L135,L144
L146          1 S L145 AND OTIT?/BIX
L147         70 S L131,L132,L142 NOT L145
L148          7 S L147 AND OTIT?/BIX
L149          3 S L147 AND (TYMPAN? OR AUDITORY CANAL OR MIDDLE EAR OR OTORRH?)
L150         16 S L147 AND EAR/BIX
L151         20 S L146,L148,L149,L150

     FILE 'WPIX' ENTERED AT 15:48:50 ON 21 JUN 2005

=>
```